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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: VIAGRA (SILDENAFIL CITRATE)
AND CIALIS (TADALAFIL) PRODUCTS
LIABILITY LITIGATION

Case No. 3:16-md-02691-RS

MDL No. 2691

This Document Relates to:

ALL ACTIONS

**DEFENDANTS PFIZER AND LILLY'S
MOTION TO EXCLUDE PLAINTIFFS'
EXPERTS' OPINIONS; MEMORANDUM
OF POINTS AND AUTHORITIES IN
SUPPORT THEREOF**

Date: June 4-7, 2019

Time: 10:00 a.m.

Judge: Honorable Richard G. Seeborg,
Courtroom 3

PLEASE TAKE NOTICE that Defendants Pfizer Inc. (“Pfizer”) and Eli Lilly and Company (“Lilly”) hereby move pursuant to Federal Rule of Evidence 702 and this Court’s Pretrial Order No. 6 to exclude the opinions of experts designated by the Plaintiffs’ Steering Committee (“PSC”) with respect to general causation, *i.e.*, whether ingestion of Viagra or Cialis can cause the progression of melanoma.

Defendants move to exclude Plaintiffs’ experts’ opinions on the grounds that they are unreliable and irrelevant and therefore inadmissible under Rule 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). This Motion is based on the attached Memorandum of Points and Authorities, the Declaration of Loren H. Brown submitted herewith, the Joint Exhibits submitted by the Parties, the hearing on this Motion, the record in this case, and such other matters as the Court may properly consider. *See* Fed. R. Civ. P. 10(c).

Dated: January 11, 2019

Respectfully submitted,

BY: /s/ Loren H. Brown

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INTRODUCTION

For nearly 20 years, tens of millions of patients relied on PDE5 inhibitor medications, such as Viagra and Cialis, to treat erectile dysfunction, pulmonary arterial hypertension, and other medical conditions. In that time, these medications were studied extensively and repeatedly found to be safe and effective. Nobody in the medical, scientific, or regulatory communities raised concern that they may be linked to melanoma.

In 2014, however, researchers conducting a small observational study (the Li study) hypothesized for the first time that PDE5 inhibitor medications may be linked in some way to melanoma. Given the significant limitations of their preliminary data, these researchers were careful to emphasize that their “study cannot prove cause and effect”; instead, they recommended additional studies and they warned that their data “should be interpreted cautiously and are insufficient to alter current clinical recommendations.” (Li et al., JAMA INTERN. MED. 2014;174(6):964-70, Joint Ex. (“JX”) 90, at 969.)

Shortly following publication of the Li study, several Plaintiffs’ law firms failed to heed the caution urged by the study’s authors and began soliciting men to file lawsuits alleging that Viagra or Cialis use “caused and/or exacerbated” their melanoma. (*See, e.g., Parker, et al. v. Pfizer, Inc.*, No. 1522-CC00318 (Mo. Cir. Ct. Feb. 9, 2015), DX 36.) These law firms then began filing lawsuits in early 2015, which led to the creation of this MDL.

Outside the courtroom, the medical, scientific, and regulatory communities took a more deliberate approach, carefully studying the issue over the next several years and ultimately finding no causal link between these medications and melanoma. Five larger and more robust observational studies published after the Li study *uniformly* failed to show any causal relationship and in fact concluded that the weak statistical associations seen in some (but not all) of the studies were attributable to underlying differences (principally relating to sun exposure) between men who took PDE5 inhibitors and men who did not. Drug safety regulators at the U.S. Food & Drug Administration (“FDA”) and European Medicines Agency (“EMA”) also evaluated the totality of available data, likewise concluding that any weak statistical associations did not reflect a causal relationship, and recommended no changes in the way these medications are labeled, prescribed,

1 or used in clinical practice. Multiple medical organizations did the same: they examined the
2 available evidence, concluded that it was insufficient to suggest a causal relationship, and declined
3 to alter treatment guidelines for physicians who prescribe these medications to their patients.

4 The extensive research and scrutiny that took place in the years following the Li study
5 demonstrate that science worked exactly as it is supposed to work. Researchers generated a
6 hypothesis based on preliminary data, appropriately cautioned other scientists about the limits of
7 their data, and encouraged attempts to replicate their results. Other scientists then conducted
8 additional studies to test the hypothesis, subjecting those studies to peer review so that the broader
9 scientific community could evaluate the hypothesis further and accept or reject its validity. In
10 *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993), the Supreme Court recognized
11 the essential role this scientific process plays in evaluating the reliability of an expert's opinion,
12 and noted the importance of general acceptance in evaluating the admissibility of expert
13 testimony. 509 U.S. at 594. That same process unfolded here, and, as a result, there are no
14 medical organizations or regulators suggesting that PDE5 inhibitors are linked to melanoma.

15 Plaintiffs' experts have taken a decidedly different position. Their opinions "do not, to
16 understate the point, reflect the consensus within the scientific community." *Daubert v. Merrell*
17 *Dow Pharms., Inc.*, 43 F.3d 1311, 1314 (9th Cir. 1995) (*Daubert II*). And it is not just that
18 Plaintiffs' experts' opinions are not "generally accepted"; they are not accepted at all, anywhere.
19 Where, as here, an expert "claims to rely on a method practiced by most scientists, yet presents
20 conclusions that are shared by no other scientist, the district court should be wary that the method
21 has not been faithfully applied." *In re Nexium Esomeprazole*, 662 F. App'x 528, 530 (9th Cir.
22 2016) (quoting *Lust ex rel. Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 598 (9th Cir. 1996));
23 see *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 197 n.4 (5th Cir. 1996) (noting that where a causal
24 relationship is not generally accepted, but an expert offers a causation opinion nonetheless, a court
25 should "particularly pay close attention" before allowing the expert to "embark upon a sea of
26 scientific uncertainty") (quoting *Braun v. Lorillard Inc.*, 84 F.3d 230, 235 (7th Cir. 1996)). This
27 complete lack of general acceptance is just the tip of the iceberg, as Plaintiffs' experts' opinions
28 raise several other red flags under *Daubert*.

1 ***Conflicting Theories Among Plaintiffs’ Experts.*** Plaintiffs’ six experts offer conflicting
 2 theories about the purported effect they believe PDE5 inhibitors have on melanoma. Plaintiffs
 3 originally alleged that PDE5 inhibitors increased the “risk of developing or exacerbating
 4 melanoma.” (Master Compl., ECF No. 98, ¶¶ 27, 32.) But Plaintiffs’ experts now all agree that
 5 PDE5 inhibitors do not cause melanoma to develop – that is, they do not initiate the cancer
 6 process by causing the genetic mutations that turn non-cancerous skin cells into melanoma cells.
 7 Rather, Plaintiffs’ experts now opine that PDE5 inhibitors affect only men who *already* have
 8 melanoma by causing their melanomas to “progress,” a concept that Plaintiffs’ experts refer to as
 9 “melanoma progression.” And they all suggest that ingestion of a *single pill* can have this
 10 “progression” effect at any time, even more than a decade after a patient took a PDE5 inhibitor.

11 Yet, even as to this narrowed theory, Plaintiffs’ experts are unable to agree on what exactly
 12 melanoma “progression” means. Some opine that Viagra and Cialis can cause a patient’s
 13 melanoma to “invade” more deeply into the skin or spread to other organs. Others opine that the
 14 medications can cause a patient’s melanoma to invade *and* “grow,” meaning that the individual
 15 tumor cells either become larger or they proliferate in number. And one expert asserts that Viagra
 16 and Cialis can promote tumor invasion (but not growth) in patients with a certain genetic
 17 mutation, and tumor growth (but not invasion) in patients without that mutation. This discord
 18 among Plaintiffs’ experts is, on its own, a strong indicator of unreliability.

19 If this all seems difficult to keep straight, the Court would not be alone in that view. On at
 20 least two occasions, Plaintiffs’ experts became so confused at their depositions that Plaintiffs’
 21 counsel took the remarkable step of prompting them to disclaim their deposition testimony and
 22 urge this Court to rely instead on the words of their lawyer-synchronized reports. (*See* Liu-Smith
 23 Tr., JX 63, at 347:1-9; Piazza Tr., JX 61, at 506:14-507:6.) Another one of Plaintiffs’ experts
 24 offered a “growth” theory in his report, then retracted that theory at his deposition, only to retract
 25 his retraction in his post-deposition “errata,” presumably after conferring with Plaintiffs’ counsel.
 26 (*See* Ganesan Tr., JX 56, at 29:22-24, 31:17-19, 51:19-23, 78:15-79:6; Ganesan Errata, JX 57, at
 27 1-3.) In the end, one needs a scorecard to keep track of these varying positions:
 28

Table 1: Plaintiffs' Experts' Conflicting Theories

	Initiation	Invasion Only	Invasion and Growth	Invasion only in BRAF+ Growth only non-BRAF+
Complaint	√		√	
Singh		√		
Ahmed			√	
Liu-Smith				√
Piazza			√	
Ganesan		√ (deposition)	√ (errata)	
Haq			√	

These inconsistent and ever-changing theories raise a significant red flag under *Daubert*.

Interpreting Studies Contrary to Studies' Own Authors. Plaintiffs' experts repeatedly offer opinions based on scientific literature that go well beyond the conclusions reached by the authors themselves. The authors of all six observational studies that have evaluated PDE5 inhibitor use and melanoma stated explicitly that their results should not be read to establish causation – and, in five of the six studies, that their results are *inconsistent* with a causal relationship. Yet, Plaintiffs' experts claim these studies all support their opinions.

The study authors also universally cautioned that the weak statistical associations between PDE5 inhibitor use and melanoma observed in some of the studies likely is attributable to underlying differences between men who took PDE5 inhibitors and men who did not. For example, the data show that PDE5 inhibitor users had more sun exposure, were of higher socioeconomic status, and were more likely to see their doctors. Thus, the authors concluded that the small association reported in some studies likely was unrelated to use of Viagra or Cialis, and instead was due to underlying differences in prior sun exposure (a common phenomenon known as “confounding,” which is pervasive in observational studies) and/or how likely the men were to have their melanomas detected (a phenomenon known as “detection bias”).

Critically, all of the studies published after the Li study also included careful analyses to help determine whether the statistical associations they observed were in fact causal – analyses the

Li study authors were unable to perform due to the limitations of the data source they studied. For example, the later studies evaluated whether there was a dose-response relationship between PDE5 inhibitor use and melanoma – in other words, whether the incidence of melanoma (the “response”) increased as the dose of Viagra or Cialis the men took increased – because dose is “the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect.” David Eaton, *Scientific Judgment and Toxic Torts: A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & POL’Y 5, 11 (2003). As Plaintiffs’ experts admit, the studies found no such relationship. The later studies also considered whether more advanced melanomas occurred more frequently in men who took PDE5 inhibitors, as one would expect if (as Plaintiffs’ experts’ opine) the medications can accelerate the “progression” of an existing melanoma. Those analyses found just the opposite: men who took PDE5 inhibitors were *less* likely to have advanced melanomas than men who did not.

In sum, Plaintiffs’ experts claim causation where the peer-reviewed literature expressly disclaims it, even though it is “axiomatic that causation testimony is inadmissible if an expert relies upon studies [or] publications, the authors of which were themselves unwilling to conclude that causation had been proven.” *Happel v. Walmart Stores, Inc.*, 602 F.3d 820, 826 (7th Cir. 2010) (*quoting Huss v. Gayden*, 571 F.3d 442, 459 (5th Cir. 2009)); *see also In re Accutane Prods. Liab.*, No. 8:04-md-2523, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009), *aff’d* 378 F. App’x 929 (11th Cir. 2010) (“when an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study”); *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 17-md-2767, 2018 WL 5276431, at *22 (S.D.N.Y. Oct. 24, 2018) (same). Because Plaintiffs’ experts repeatedly draw conclusions from studies that the study authors do not, the Court “may conclude that there is simply too great an analytical gap between the data and the opinion proffered.” *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Unreliable Application of Bradford Hill Criteria. Plaintiffs’ three epidemiology experts try to bridge the “analytical gap” in their opinions by invoking the “Bradford Hill” criteria, which are “metrics that epidemiologists use to distinguish a causal connection from a mere association.” *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795 (3rd Cir. 2017).

1 These criteria, however, involve the selective weighing of multiple factors, and as such under
 2 *Daubert*, the Court must ensure “that the Bradford Hill/weight of the evidence criteria ‘is truly a
 3 methodology, rather than a mere conclusion-oriented selection process.’” *Id.* at 796-800 (internal
 4 citation omitted) (affirming exclusion of “conclusion-driven” analysis); *Soldo v. Sandoz Pharms.*
 5 *Corp.*, 244 F. Supp. 2d 434, 514 (W.D. Pa. 2003) (excluding experts whose “efforts to apply the
 6 Bradford Hill principles” were “not scientifically reliable”).

7 Plaintiffs’ experts do not reliably apply the Bradford Hill methodology, but instead employ
 8 an entirely results-oriented approach. That is, when Bradford Hill criteria do not support their
 9 opinions, Plaintiffs’ experts claim those criteria are unimportant or not required, and when
 10 Bradford Hill criteria do (according to them) support their opinions, they say those criteria are the
 11 most important and suggestive of a causal relationship. This is a conclusion-driven process that
 12 does not reflect “the same level of intellectual rigor that characterizes the practice of an expert in
 13 the relevant field.” *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

14 ***Failing to Subject Their Courtroom Opinions to Peer Review.*** Plaintiffs’ experts have
 15 not sought to publish their analyses or otherwise subject them to peer review. To the contrary, one
 16 of Plaintiffs’ experts, Dr. Gary Piazza, has published precisely the opposite of what he now claims
 17 in this lawsuit. (*See infra* Statement of Facts [“SOF”] § II.D.) And most of Plaintiffs’ experts
 18 could not recall even sharing with their colleagues that they believed PDE5 inhibitors cause
 19 melanoma progression. “[S]ubmission to the scrutiny of the scientific community is a component
 20 of ‘good science,’ in part because it increases the likelihood that substantive flaws in methodology
 21 will be detected.” *Daubert*, 509 U.S. at 593. That Plaintiffs’ experts’ analyses have not
 22 undergone peer review, and differ from the interpretations of the authors whose published studies
 23 have been peer reviewed, is yet another indication that their methodologies and opinions are
 24 unreliable. *See Carnegie Mellon Univ. v. Hoffmann-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1033-34
 25 (N.D. Cal. 1999) (“absence of peer-reviewed publication is another factor in favor of excluding
 26 [expert] testimony”).

27 ***Dismissing Entire Bodies of Contradictory Data.*** Plaintiffs’ experts dismiss a large body
 28 of research spanning more than 20 years in which scientists have tested PDE5 inhibitors as

1 *treatments* for melanoma and other cancers, and found either no effect or that the medications
 2 actually reduced the growth of those cancers. One of the most active authors in this field is
 3 Plaintiffs' own expert, Dr. Piazza, who as recently as 2017 proposed that Viagra and Cialis should
 4 be tested as therapeutic agents for fighting or preventing cancer, and who has obtained multiple
 5 patents expressly claiming – based on his own studies – that PDE5 inhibitors may be used to
 6 prevent and to treat melanoma and other cancers. Plaintiffs' experts also ignore or dismiss – with
 7 no reliable scientific basis – ongoing research by other scientists using PDE5 inhibitors to treat
 8 cancers, including clinical trials in humans that have produced promising results, and which
 9 Plaintiffs' experts agree would be unethical to conduct if there were reliable evidence that PDE5
 10 inhibitors cause melanoma progression.

11 ***Unreliable Biological Plausibility Opinions.*** As claimed support for their causation
 12 opinions, Plaintiffs' experts opine that it is “biologically plausible” that PDE5 inhibitors can
 13 increase melanoma progression. But biological plausibility is “not proof of causation.” *In re*
 14 *Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1296 (M.D. Fla. 2007), *aff'd sub nom Rand v.*
 15 *Hoffmann-LaRoche Inc.*, 291 F. App'x 249, 251 (11th Cir. 2008). At least one of Plaintiffs'
 16 biology experts, Dr. Haq, recognizes that limitation and expressly declines to offer any opinion on
 17 causation. (Haq Tr., JX 58, at 48:7-15, 78:4-10, 248:23-249:16.)

18 In any event, Plaintiffs' experts' biological plausibility opinions are unreliable. Plaintiffs'
 19 experts primarily cite two papers to support those opinions, but again offer interpretations of the
 20 data not shared by those who performed the actual research. For example, Plaintiffs' experts rely
 21 on one cherry-picked experiment out of dozens in a 2011 preclinical study (the Arozarena study).
 22 The study's lead author, Dr. Richard Marais – whom Plaintiffs' experts consistently praise as one
 23 of the world's leading melanoma researchers – and his colleagues concluded based on their
 24 experiments, however, that Viagra “did not increase tumor burden” in mice and that “we do not
 25 perceive [PDE5 inhibitor use] to be a problem.” (Arozarena et al., *CANCER CELL* 2011;19(1):45-
 26 57, JX 85, at 53-55.) In fact, upon learning that Plaintiffs relied on his work in support of their
 27 lawsuits, Dr. Marais was “indignant” about the mischaracterization of his lab's results and agreed
 28 to serve as a defense expert. (Marais Tr., JX 71, at 225:4-19.) Plaintiffs' experts also extrapolate

1 results from one other preclinical study (the Dhayade study), even though they recognize that
 2 experiments in petri dishes and mice cannot reliably predict human responses, *see In re Mirena*,
 3 2018 WL 5276431, at *11, and despite other significant, acknowledged study limitations.

4 *****

5 In sum, Plaintiffs' experts' opinions are unreliable, methodologically unsound, and lack
 6 the indicia of "good science" required by *Daubert*. Their opinions do not satisfy the *Daubert*
 7 hallmarks of reliable methods – they are not generally accepted, go well beyond (or contradict) the
 8 conclusions drawn by the authors of the studies on which the experts rely, and have not been
 9 subject to peer review. Their opinions are further based on unreliable analyses of the clinical trial
 10 and observational study data – the experts ignore clinical trials altogether, do not reliably assess
 11 confounding and bias in the observational studies, and do not reliably apply the Bradford Hill
 12 criteria. If the Court excludes those causation opinions, then it need not reach the narrower
 13 biological plausibility opinions. Those too, however, are unreliable and subject to exclusion.
 14 They are based on cherry-picked findings from the available animal and petri dish experiments,
 15 which involve models that do not apply to humans, used massive doses of PDE5 inhibitors, and/or
 16 did not test PDE5 inhibitors alone.

17 The Court should exclude the opinions of Plaintiffs' experts in their entirety.

18 **STATEMENT OF FACTS**

19 **I. CHRONOLOGY OF RELEVANT EVENTS**

20 **A. Melanoma Is A Serious Skin Cancer With Multiple Well-Established Risk** 21 **Factors, Most Notably Sun Exposure.**

22 Melanoma is a serious and potentially fatal form of skin cancer. (Ganesan Rep., JX 17, at
 23 2.) Fortunately, the majority of patients are diagnosed with early stage melanoma (Stages 0-I),
 24 which can be cured by surgically removing the tumor. (Schuchter Rep., JX 30, at 1.) Patients
 25 with later stage melanoma (Stages II-IV) have an increased risk of metastasis to other organs.
 26 (*Id.*) Although its incidence is rising worldwide, melanoma is less common than other skin
 27 cancers, such as basal cell carcinoma and squamous cell carcinoma. (Ganesan Rep., JX 17, at 2.)
 28

1 Like other cancers, melanoma arises from DNA mutations that turn a healthy cell into a
 2 malignant one that grows and divides uncontrollably. (Haq Rep., JX 9, at 3.) Melanoma arises
 3 from melanocytes, which are skin cells that produce melanin, the pigment responsible for skin
 4 color. (Ganesan Rep., JX 17, at 9.) Approximately 50% of all melanoma cells have a mutation in
 5 a gene known as BRAF, and approximately 25% of all melanoma cells have a mutation in a gene
 6 known as NRAS. (*Id.* at 11-12.) Those mutations affect how the body signals cells to grow,
 7 divide, or die, through a process known as the mitogen-activated protein kinase (“MAPK”)
 8 pathway. (*Id.*) In healthy cells, the MAPK pathway turns off and on according to the body’s
 9 normal needs. In cells with melanoma-related mutations, however, the MAPK pathway is turned
 10 on (“activated”) indefinitely and sends signals to the melanocyte to grow uncontrollably,
 11 contributing to the development of melanoma. (*Id.*)

12 There are well-established risk factors for melanoma. Ultraviolet (“UV”) light exposure is
 13 “[t]he major identified risk factor for melanoma.” (Haq Rep., JX 9, at 10.) UV exposure from any
 14 source (natural sunlight, artificial sunlamps, or tanning beds) “creates mutations within genes that
 15 lead to uncontrolled melanocyte growth or invasion.” (*Id.*; *see also* Haq Tr., JX 58, at 56:11-
 16 57:2.) Some “melanomas can develop after long term UV exposure while others can develop from
 17 moles (pre-cancers) after short bursts of UV exposure.” (Ganesan Rep., JX 17, at 11.) “The time
 18 from environmental exposure to onset of the disease is lengthy (typically many years to decades), .
 19 . . .” (Haq Rep., JX 9, at 10.)

20 Other risk factors include family history of melanoma, light skin color, number of moles,
 21 and taking medicines that suppress the immune system. (Ahmed Tr., JX 65, at 34:9-35:9; Haq Tr.,
 22 JX 58, at 225:20-226:13.) Plaintiffs’ experts agree there is no medical, scientific, or regulatory
 23 body that identifies PDE5 inhibitor use as a risk factor, and they concede that no test or
 24 examination can show that an individual patient’s melanoma was made to “progress” by a PDE5
 25 inhibitor. (Ahmed Tr., JX 65, at 82:1-10, 172:16-173:1, 401:16-22; Ganesan Tr., JX 56, at 74:15-
 26 20, 81:17-83:11; Haq Tr., JX 58, at 238:2-12, 265:16-266:3; Liu-Smith Tr., JX 63, at 82:20-88:15;
 27 Piazza Tr., JX 60, at 33:16-24; Piazza Tr., JX 61, at 428:16-430:2; Singh Tr., JX 54, at 82:14-18,
 28 120:12-121:7.)

B. For More Than 20 Years, Viagra And Cialis Have Been Safe and Effective Treatment Options For Tens of Millions Of Men With Erectile Dysfunction.

Viagra (also known by its molecular name sildenafil) and Cialis (tadalafil) are oral medications approved by FDA for the treatment of erectile dysfunction, which affects as many as 30 million men in the U.S. and 150 million men worldwide. (Viagra Label, Dec. 14, 2017, DX 1, at 1; Cialis Label, Feb. 15, 2018, DX 2, at 1; Burnett et al., AUA Educ. & Research, Inc., Erectile Dysfunction: AUA Guideline, Apr. 2018, DX 3, at 7.) They are part of a class of medications known as phosphodiesterase-5 (“PDE5”) inhibitors. PDE5 inhibitors cause an erection by increasing the amount of blood flow into the penis. (Viagra Label, DX 1, at 12.) Normally, sexual stimulation increases levels of a chemical called cyclic guanosine monophosphate (“cGMP”) in the penis, which allows for the inflow of blood and an erection. (*Id.*) Men with erectile dysfunction do not have sufficient cGMP levels to have an erection. PDE5 inhibitors work by blocking an enzyme called PDE5, which ordinarily degrades cGMP. (*Id.*) When the PDE5 enzyme is blocked by a PDE5 inhibitor, the PDE5 enzyme cannot degrade cGMP, so there is an increase in cGMP in the penis, which enables the blood flow necessary for an erection. (*Id.*)

Viagra Approval. In March 1998, FDA approved Viagra after evaluating more than 300 volumes (totaling more than 170,000 pages) of scientific evidence, including 30 toxicology studies and 21 clinical trials involving approximately 4,500 men. (FDA Approval Letter for Viagra, Mar. 27, 1998, DX 8; *see generally* Center for Drug Evaluation and Research, VIAGRA Drug Approval Package, DX 4.) None of the preclinical studies (studies in petri dishes and animals) showed that Viagra is mutagenic (causes changes to DNA) or carcinogenic (causes cancer). (Pfizer Response to PRAC Request for Supplementary Information [“Pfizer Response to PRAC Request”], DX 5, at 15.) The toxicology studies, which involved thousands of animals and multiple different species, also showed no evidence of melanoma. (*See* Sildenafil Toxicopharmacological Expert Report, Appendix 4, DX 6.)

Similarly, none of the 21 pre-approval clinical trials showed an association with melanoma. (Pfizer Response to PRAC Request, DX 5, at 15-20.) Eleven of the trials were double-blind, placebo-controlled trials, which are the “gold standard for determining the

relationship of an agent to a health outcome or adverse side effect.” (REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 3d ed., 2011 [“REF. MAN.”], at 555.) Many of the men in the clinical trials elected to participate in additional, open-label extension studies that lasted for up to four years. (Goldstein et al., SEX MED. REV. 2018; 1-14, DX 7, at 7.) After reviewing eight years’ worth of research, FDA determined that Viagra “is safe and effective for use as recommended” in the product label. (FDA Approval Letter for Viagra, DX 8, at 1.)

Cialis Approval. FDA approved Cialis to treat erectile dysfunction through as-needed use in November 2003, to treat erectile dysfunction through once-daily use in January 2008, and again for treatment of an enlarged prostate condition known as benign prostatic hyperplasia, either alone or with erectile dysfunction, in October 2011. (FDA Approval Letter for Cialis, Nov. 21, 2003, DX 9; FDA Supplemental Approval Letter for Cialis, Jan. 7, 2008, DX 10; FDA Supplemental Approval Letter for Cialis, Oct. 6, 2011, DX 11; Cialis Label DX 2, at 2.) Lilly tested the medication for these indications in over 75 clinical studies enrolling almost 25,000 men, as well as in dozens of studies in petri dishes and animals. (Lilly Safety Topic Report: Prostate, Bladder, and Skin Cancer, Dec. 2, 2014, DX 12, at 27, 29-32.) As with Viagra, none of the preclinical studies suggested that Cialis is mutagenic or carcinogenic. (*Id.* at 27-28.) The toxicology studies likewise showed no evidence of melanoma. (*Id.*) Similarly, none of the clinical trials, over 50 of which were double-blind and placebo-controlled, showed an association with melanoma. (*Id.* at 29-30; Lilly Safety Topic Report: Melanoma, Dec. 2, 2016 [“Lilly 2016 Safety Topic Report”], DX 13, at 39.)

Dosing for Erectile Dysfunction. For erectile dysfunction, both Viagra and Cialis are primarily taken as needed. The recommended dose of Viagra is one 50 mg tablet, but 25 mg and 100 mg tablets also are available. (Viagra Label, DX 1, at 2.) The recommended dose of Cialis for as-needed use is one 10 mg tablet, but 5 mg and 20 mg tablets are also available. (Cialis Label, DX 2, at 2.) Cialis also may be taken once daily at either 2.5 mg or 5 mg. (*Id.*)

Additional Indications. PDE5 inhibitors have been approved for a number of indications beyond erectile dysfunction. In June 2005, FDA approved sildenafil under the brand name Revatio for daily use by men and women for the treatment of pulmonary arterial hypertension

1 (“PAH”), a chronic, progressive, and often life-threatening type of high blood pressure in the
 2 arteries of the lungs. (FDA Approval Letter for Revatio (June 3, 2005), DX 14, at 1; Revatio
 3 Label, Feb. 1, 2018, DX 15, at 1.) In May 2009, FDA approved tadalafil for the treatment of PAH
 4 under the brand name Adcirca. (FDA Approval Letter for Adcirca (May 22, 2009), DX 16, at 1;
 5 Adcirca Label, May 5, 2017, DX 17, at 1.) No patients in any of the Revatio or Adcirca clinical
 6 trials developed melanoma. (Pfizer Response to PRAC Request, DX 5, at 20-23; Lilly 2016
 7 Safety Topic Report, DX 13, at 37.)

8 Today, more than 45 million men have taken at least one Viagra pill and more than 57
 9 million men have used Cialis. (Goldstein, DX 7, at 8, Tbl. 3; Lilly 2016 Safety Topic Report, DX
 10 13, at 10.) Combined, Pfizer and Lilly have studied sildenafil and tadalafil in clinical trials
 11 involving more than 60,000 men and women. (*Id.*) Over approximately 20 years of widespread
 12 use, Viagra and Cialis have remained safe and effective medications, without any suggestion of a
 13 link to melanoma.

14 **C. For More Than 20 Years, Researchers Have Studied PDE5 Inhibitors For The**
 15 **Treatment Of Cancer, Including Melanoma.**

16 Since at least 1997, researchers have studied PDE5 inhibitors for other promising uses,
 17 including cancer treatment. (*See, e.g.,* Piazza et al., U.S. Patent No. 5,858,694, DX 18, at 1.)
 18 More than 15 published preclinical studies tested the effects of PDE5 inhibitors in cells or animal
 19 models of lung cancer, breast cancer, prostate cancer, brain cancer, colorectal cancer, colon
 20 cancer, lymphoma, soft tissue sarcoma, thyroid carcinoma, and melanoma.¹ None of these studies

21
 22 ¹ *See, e.g.,* Domvri et al., J CANCER 2017;8(18):3648-56 (lung cancer), DX 19; Booth et al.,
 23 ONCOTARGET 2017;8(1):1449-68 (lung cancer), DX 20; Confino et al., CANCER IMMUNOL
 24 IMMUNOTHER. 2016;65(10):1149-58 (breast cancer), DX 21; Tavallai et al., J CELL PHYSIOL.
 25 2015;230(9):2281-98 (liver and colon cancer), DX 22; Black et al., BRAIN RES. 2008;1230:290-
 26 302 (brain cancer), DX 23; Sharman et al., CANCER PREV RES. 2018;11(2):81-92 (colorectal
 27 cancer), DX 24; Qian et al., J UROL. 2003;170:994-97 (prostate cancer), DX 25; Roberts et al.,
 28 ONCOTARGET 2017;8(59):99451-469 (colon cancer), DX 26; Serafini et al., CANCER RES.
 2008;68(13):5439-49 (lymphoma), DX 27; Serafini et al., J EXP MED. 2006;203:2691-702 (colon
 carcinoma, melanoma), JX 116; Greish et al., J DRUG TARGET 2018;26(7):610-15 (breast cancer),
 DX 28; Islam et al., CANCER PREV RES. 2017;10(7):377-88 (colorectal cancer), DX 29; Zenitani et
 al., CANCER MED. 2016;5(5):795-805 (soft tissue sarcoma), DX 30; Mei et al., AM J CANCER RES.

1 showed that PDE5 inhibitors caused or worsened cancer, and many have reported that PDE5
2 inhibitors may be beneficial for cancer treatment.

3 Indeed, in May 1997, before FDA approved Viagra or Cialis, Plaintiffs' expert Dr. Piazza
4 filed a patent application (awarded in 1999) in which he claimed to have discovered "a
5 relationship between inhibition of cancer and inhibition of . . . PDE5" that could be used to
6 develop treatments to inhibit "a precursor to malignant melanoma," as well as established
7 melanomas. That patent was supported by other results showing PDE5 inhibition deterred the
8 growth of melanoma, lung, breast, and other cancer cells. (*Id.* at 18.) Dr. Piazza since has
9 submitted at least five patent applications and published multiple scientific articles advocating
10 PDE5 inhibitor use to prevent and treat melanoma and other cancers, supported by more than 15
11 years of laboratory data reporting anti-cancer effects. (Piazza CV, JX 7, at 6-15, 30-34; Piazza
12 Tr., JX 61, at 338:25-340:20, 341:6-342:14, 444:7-446:2, 447:7-449:12.)

13 Multiple other researchers have published findings of anti-cancer effects of PDE5
14 inhibitors. One of the reasons cancers grow uncontrollably is that they evade the body's natural
15 immune system, which ordinarily would attack and clear cancer cells from the body. Researchers
16 have demonstrated that PDE5 inhibitors may help reverse this process. For example, studies
17 published in 2006 and 2011 investigated whether PDE5 inhibitors can reduce melanoma growth
18 by reversing a melanoma tumor's ability to evade the body's immune system. (Serafini, JX 116;
19 Meyer, JX 110.) These studies showed that PDE5 inhibitors reverse some of the
20 immunosuppressive mechanisms of melanoma in cells and mice, with melanoma-bearing mice
21 experiencing increased survival with exposure to PDE5 inhibitors. (*Id.*) These studies were
22 followed more recently by clinical trials in which human patients with advanced melanoma or
23 head and neck squamous cell cancers were treated with PDE5 inhibitors in combination with other
24 therapies. Each trial reported anti-cancer effects. (*See infra* SOF § I.I.)

25 2015;5(11):3311-24 (colorectal cancer), DX 31; Das et al., PROC NATL ACAD SCI USA
26 2010;107(42):18202-07 (prostate cancer), DX 32; Sponziello et al., ENDOCRINE 2015;50(2):434-
27 41 (thyroid carcinoma), DX 33; Meyer et al., PROC NATL ACAD SCI USA 2011;108:17111-116
28 (melanoma), JX 110.

D. In 2011, The Arozarena Study Concluded That PDE5 Inhibitors Did Not Promote Melanoma In Animals And That Their Use “Was Not A Problem.”

In 2011, a study published by Dr. Marais and his colleagues (the Arozarena study) investigated whether the PDE5 gene (which makes the PDE5 enzyme) plays a role in the MAPK signaling pathway in melanoma cells. (Arozarena, JX 85.) The study reported the findings of more than 50 cell and animal experiments, but because the main focus of the study was understanding the role of the PDE5 gene itself only a handful of those experiments involved PDE5 inhibitors. (*Id.*)

Among that handful of experiments involving PDE5 inhibitors, a single experiment in a petri dish (known as an *in vitro* experiment) using melanoma cells with a mutated BRAF gene reported that the cells became more “invasive” when treated with either Viagra, Cialis, or Levitra. (*Id.* at 50, Fig. 4E.) “Invasion” was nothing more than a measure of cell movement; the results were limited to melanoma cells from a single patient who already had advanced, metastatic disease; and the Arozarena authors could not replicate the results in several other experiments using melanoma cells from other patients, including those with and without the BRAF mutation. (*Id.* at 50, Fig. 4G; Suppl. Fig. S2.) The results also were not replicated when the Arozarena authors conducted an experiment in live mice (known as an *in vivo* experiment), in which there was no increase in the tumor burden in the lungs of the mice. (*Id.* at 54, Fig. 7K.) For this reason, and because PDE5 inhibitors are often taken as needed and their effects are short-lived, the researchers did “not perceive [the use of PDE5 inhibitors] to be a problem” (*id.* at 55), and cautioned that their “data should be interpreted with care” and do “not immediately suggest that PDE5A inhibitors will drive melanoma metastasis.” (*Id.*)

When published, the Arozarena study received little attention from the medical, scientific, and regulatory communities. There were no changes to clinical practice guidelines regarding PDE5 inhibitor use in patients with melanoma or at risk of melanoma, no statements issued by any public health authorities, and no inquiries posed by any regulatory agencies. Upon learning that Plaintiffs were placing principal reliance on his study in support of their melanoma progression theory, Dr. Marais, the senior author of the study and one of the world’s leading experts in

1 melanoma research, was “indignant” about the mischaracterization of his lab’s work and agreed to
 2 serve as a defense expert, the first time he has ever testified as an expert in litigation. (Marais Tr.,
 3 JX 71, at 79:6-24, 225:4-19.)

4 **E. In 2014, The Li Study Raised Questions About A Possible Association Between**
 5 **PDE5 Inhibitor Use And Melanoma.**

6 In April 2014, three years after the Arozarena study was published, an observational study
 7 by Li et al. reported a statistically significant association between Viagra use and melanoma.² (Li,
 8 JX 90, at 964.) The Li study examined an existing database of survey responses from male health
 9 professionals that had been compiled years before for other purposes. In the responses, the men
 10 had self-reported (among many other things) their Viagra use as of a single point in time in 2000;
 11 the Li authors then identified new diagnoses of melanoma in those men occurring over the next ten
 12 years. (*Id.* at 965; Singh Tr., JX 54, at 203:10-13.) The researchers did not confirm Viagra use
 13 with prescription records, and they did not obtain information regarding the dose or frequency
 14 with which the study subjects used Viagra (or any other PDE5 inhibitor). (Li, JX 90, at 965;
 15 Singh Tr., JX 54, at 160:14-23, 161:17-25, 163:7-18; Singh Rep., JX 2, at 19.) Among the men
 16 who had reported recent use of Viagra in 2000, the researchers identified 14 men with new
 17 melanoma diagnoses at some point during the following decade. (Li, JX 90, at 966, 967, Tbl. 2.)
 18 Based on those 14 melanoma events, the authors reported a statistical association between recent

20 ² An epidemiological study “compares outcomes for subjects who are exposed to some factor (the
 21 treatment group) with outcomes for other subjects who are not exposed (the control
 22 group).” (REF. MAN. at 218-19.) “In a controlled experiment [a clinical trial], the investigators
 23 decide which subjects will be exposed and which subjects will go into the control group. In
 24 observational studies, by contrast, the subjects themselves choose their exposures. Because of
 25 self-selection, the treatment and control groups are likely to differ with respect to influential
 26 factors other than the one of primary interest.” (*Id.* at 219.) Statistical significance is a measure of
 27 confidence that a trend observed in a dataset is not due to chance (random error). Study findings
 28 with statistically significant results are less likely to be the result of random error. (*Id.* at 573.)
 Statistical significance is usually expressed through a p-value, which represents the probability
 that an observed association could result from random error even if no association were in fact
 present. A p-value less than 0.05 is typically considered to be a statistically significant result. (*Id.*
 at 576-77.)

1 Viagra use as of 2000 and a subsequent diagnosis of melanoma, with a relative risk of 1.84 as
2 compared to non-Viagra users. (*Id.*)³

3 The researchers recognized, however, that if the men who took Viagra differed from men
4 who did not in ways that increased the Viagra users' risk of melanoma, the results of their study
5 could be confounded by those underlying differences.⁴ The Li study acknowledged that "possible
6 differences in health status and lifestyle practices between [Viagra] users and nonusers may have
7 confounded our findings." (*Id.* at 968.) In fact, the researchers observed that Viagra use "was
8 correlated with factors that may increase melanoma diagnosis, such as more severe or blistering
9 sunburns and more physical examinations." (*Id.*)

10 While they attempted to adjust for some potential confounders, the authors could not "rule
11 out the possibility of residual confounding by unmeasured or imperfectly measured confounders."
12 (*Id.*) For example, measurements of sun exposure – such as the number of severe sunburns a
13 survey respondent reported over the course of his life – are subject to errors and biases, since it is
14 difficult for an adult to recall accurately this type of information from decades earlier. As one of
15 Plaintiffs' experts explained, "[E]xposure measurements are always crude. I mean, it's not like
16 you're going to precisely measure sun exposure. It's not something that can be done." (Singh Tr.,
17 JX 54, at 171:22-172:9.) Because they could not adequately take into account factors such as sun

18 ³ A relative risk is "[a] measure of association used in epidemiology. For example, if 10% of all
19 people exposed to a chemical develop a disease, compared to 5% of people who are not exposed,
20 then the disease occurs twice as frequently among the exposed people: The relative risk is
21 $10\%/5\% = 2$." (REF. MAN. at 295.) Researchers calculate the relative risk, or risk ratio, of
22 developing a disease by comparing the proportion of subjects in the exposed group who develop
23 the disease versus the proportion in the unexposed group who develop the disease. (*Id.* at 557-58.)
24 Similarly, an odds ratio compares the odds of having the disease in patients who were exposed to a
25 medication versus the odds of having the disease in those who were not. (*Id.* at 625.) A relative
26 risk or odds ratio of 1 indicates no association. (*Id.* at 291, 295.) Odds ratios approximate risk
27 ratios. (*See id.* at 625 ["For most purposes the odds ratio from a case-control study is quite similar
28 to a risk ratio from a cohort study."].)

⁴ Confounding arises when there are systematic differences between two groups being compared
and studied, which impact both the likelihood of using a medication and of experiencing a health
outcome. Confounding may lead to reported differences in risk between two populations that are
due to differences that existed before one population took a medication, rather than due to the
medication. (*See* REF. MAN. at 591.)

1 exposure, the Li study authors acknowledged that residual confounding could account for the
2 statistical association they observed. (Li, JX 90, at 968.)

3 Because of the limitations of their dataset, the researchers also could not adjust for any
4 differences between Viagra users and non-users in the number of times a patient was seen by a
5 doctor and received a physical examination. (*Id.* at 966.) Since men who see their doctors more
6 frequently are more likely to have suspicious lesions on their skin detected and examined, they are
7 more likely to be diagnosed with melanoma, a phenomenon known as “detection bias.”⁵

8 Based on their finding of a statistical association, the Li study concluded that “[Viagra] use
9 *may be associated* with an increased risk of developing melanoma.” (*Id.* at 964 [emphases
10 added].) The researchers cautioned that “[o]ur study cannot prove cause and effect,” and therefore
11 their findings “should be interpreted cautiously and are insufficient to alter current clinical
12 recommendations” for PDE5 inhibitor use. (*Id.* at 964, 969.) Other scientists immediately
13 recognized the limitations of the Li study. As a Harvard Medical School publication noted, “The
14 relationship could be pure coincidence. Epidemiological studies like this one tell you only who is
15 at the scene of the crime, not who done it. The findings of the [Li] study need to be replicated in
16 other groups of men before sounding any warning bells.” (Pendick, Harvard Health Blog, June 5,
17 2014, DX 34.)

18 The Li study authors agreed and advised, “Further studies are needed to confirm our
19 findings in other populations, particularly in a dose-dependent manner, and to investigate
20 underlying biological mechanisms.” (Li, JX 90, at 969.) The authors thus recognized that a key
21 question in determining whether the association they observed could be causal was whether a
22 dose-response relationship existed – that is, whether the incidence of melanoma increased as the
23

24 ⁵ Detection bias can result from differences in the way that exposures or disease outcomes are
25 measured between two comparison groups. For example, if one study group receives more
26 frequent skin examinations to screen for melanoma, this could lead to differential detection rates,
27 with systematic underestimation of melanoma in the other group at a given point in time and
28 possibly even overestimation (in the event of false positives) in the group subjected to more
frequent screening. (REF. MAN. at 588-89.)

number of PDE5 inhibitor pills taken increased. That question was investigated, and all experts agree that a dose-response relationship has not been demonstrated. (*See infra* SOF § I.F.)

In the wake of the Li study, Plaintiffs’ lawyers began advertising on television and the internet, soliciting cases. (*See, e.g.,* Charles Toutant, *Lawyers Ready Suits Claiming Viagra Caused Skin Cancer*, N.J. L.J., Nov. 13, 2014, DX 35.) By early 2015, Plaintiffs began filing lawsuits across the country alleging that their PDE5 inhibitor use “caused and/or exacerbated” melanoma. (*See, e.g., Parker, et al. v. Pfizer, Inc.*, No. 1522-CC00318 (Mo. Cir. Ct. Feb. 9, 2015), DX 36.)

F. Since 2015, Multiple Larger And Better-Designed Studies Have Not Replicated The Findings Of The Li Study And Have Concluded That The Observed Association Was Likely Due to Confounding.

Following the publication of the Li study, other researchers set out to test whether its findings could be replicated, using different healthcare databases and more robust analytical methods. Since 2015, five published observational studies – the Loeb, Lian, Matthews, Pottgard, and Shkolyar studies – have examined PDE5 inhibitor use and melanoma in much larger populations than the Li study. (Loeb et al., JAMA 2015;313(24):2449-55, JX 93;⁶ Lian et al., EUR UROL. 2016;70(5):808-15, JX 91; Matthews et al., PLOS MED. 2016;13(6):e1002037, JX 94; Pottgard et al., BR J CANCER 2016;115(7):895-900, JX 96; Shkolyar et al., J SEX MED. 2018;15(7):982-89, JX 97; *see* Appendix [“App.”], Table 3.)

None of these studies found a causal relationship between PDE5 inhibitor use and melanoma. Some did not even observe a statistical association at all; others found a small association that they universally attributed to confounding by sun exposure, socioeconomic status, or other unmeasured variables and/or detection bias. (Loeb, JX 93, at 2449; Lian, JX 91, at 808; Matthews, JX 94, at 1-2; Pottgard, JX 96, at 895; Shkolyar, JX 97, at 982, 985, Tbl. 2.) It is not surprising that the later observational studies failed to confirm the Li study’s preliminary findings,

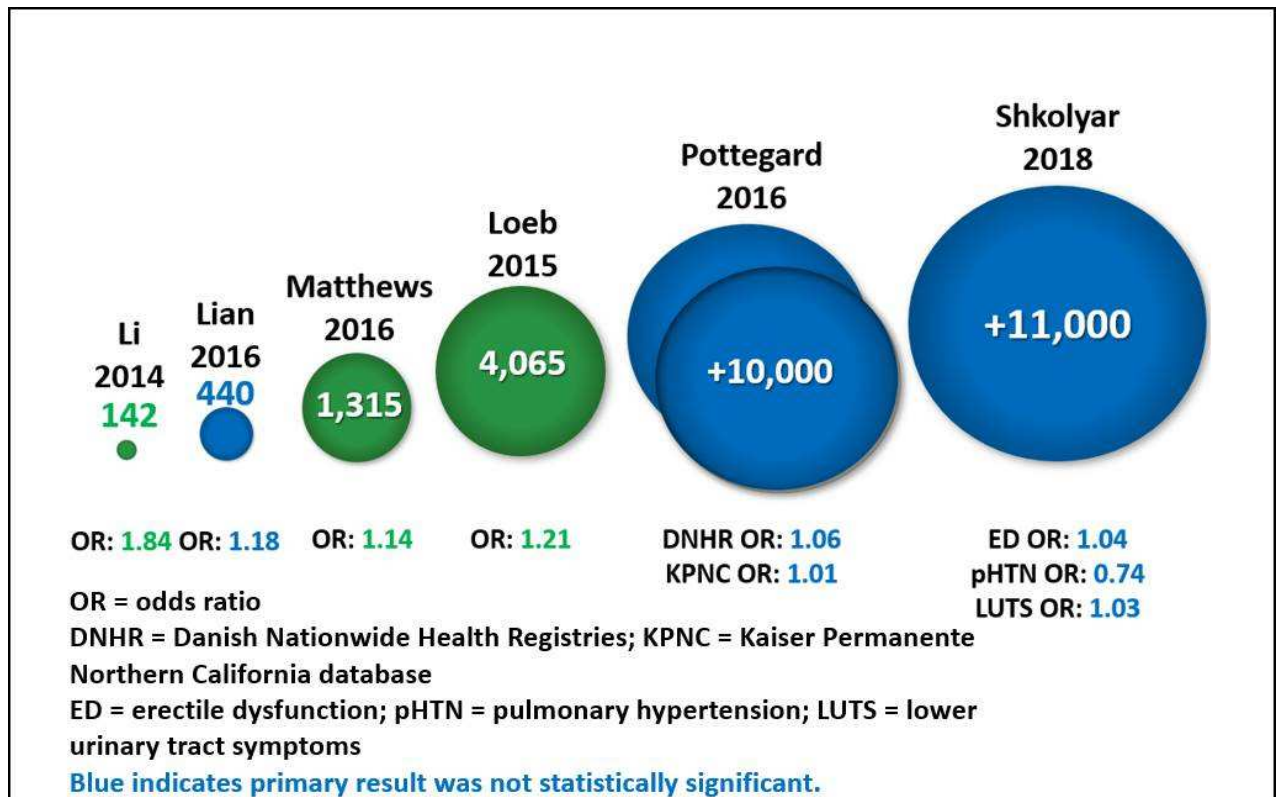
⁶ One author of the Loeb study, Dr. Stacey Loeb, was retained by Lilly as a consulting expert in 2016, following the publication of her 2015 observational study.

as “reporting of associations that are not replicated is [] a common occurrence in epidemiology.” (Boffetta et al., J NATL CANCER INST. 2008;100(14):988-995, DX 37, at 988.)

As reflected in Table 2 below, no study came close to replicating the 1.84 risk ratio reported in the Li study, and all of the study authors agreed their findings did not support or establish a causal relationship between the use of PDE5 inhibitors and melanoma.

Table 2: Estimated Risk & Author Statements in Observational Studies		
Study	Estimated Risk	Authors’ Statement Regarding Causation
Loeb	1.21	“[T]he pattern of association (eg, the lack of association with multiple filled prescriptions) raises questions about whether this association is causal.” (Loeb, JX 93, at 2449.)
Lian	1.18 (not statistically significant)	“In this study, the use of phosphodiesterase type 5 inhibitors was not associated with an increased risk of melanoma skin cancer.” (Lian, JX 91, at 808.)
Matthews	1.14	“Our results were not consistent with PDE5 inhibitors being causally associated with melanoma risk, and strongly suggest that observed risk increases are driven by greater sun exposure among patients exposed to a PDE5 inhibitor.” (Matthews, JX 94, at 2.)
Pottegard	Danish Database (DNHR): 1.06 (not statistically significant) California Database (KPNC): 1.01 (not statistically significant)	“[O]ur findings provide little support for a causal association between use of [PDE5 inhibitors] and risk of melanoma.” (Pottegard, JX 96, at 899.)
Shkolyar	1.04 (not statistically significant)	“[W]e found no evidence of a causal association between sildenafil use and melanoma.” (Shkolyar, JX 97, at 988.)

These observational studies examined larger populations with many more melanoma events than the Li study. As reflected in Figure 1 below, as the size of the study population and the number of melanoma events increased – in other words, as researchers had more information and more certainty about their estimate of any effect – the magnitude of the statistical association decreased or disappeared entirely.

Figure 1: Number of Melanomas & Odds Ratios Reported in Observational Studies

Unlike the Li study, these later observational studies also examined whether men who took higher doses of PDE5 inhibitors were at greater risk of melanoma than men who took lower doses – a factor that the Li authors acknowledged was essential to and missing from their analysis. None of the studies yielded reliable evidence of such a dose-response relationship. (Loeb, JX 93, at 2451-52; Lian, JX 91, at 810-811; Pottegard, JX 96, at 897-98.) In fact, the Loeb study observed the opposite: a small statistical association between PDE5 inhibitor use and melanoma among men who filled a single prescription for a PDE5 inhibitor, but no association among men who filled 2-5 prescriptions or greater than 6 prescriptions. (Loeb, JX 93, at 2452, Tb1. 3.)

The subsequent observational studies also provided compelling evidence that the slight differences observed in melanoma rates between PDE5 inhibitor users and non-users were likely due to baseline differences in sun exposure. The studies used what are known as “negative controls” – measurements of an outcome not hypothesized to be connected to the medicine studied (here, PDE5 inhibitors) but potentially related to an alternative causal factor (here, sun exposure). To test this sun exposure hypothesis, the authors measured other disease outcomes (basal cell

1 carcinoma, squamous cell carcinoma, and solar keratosis) understood to be driven by sun exposure
 2 but not thought to be related to PDE5 inhibitor use. If PDE5 inhibitors were biologically
 3 connected to melanoma progression, a statistical association with PDE5 inhibitors should appear
 4 in analyses of melanoma but not in analyses of these other types of sun exposure-driven diseases,
 5 each of which has unique biological drivers.⁷ On the other hand, if PDE5 inhibitors are
 6 statistically associated with both melanoma and other sun exposure-driven outcomes, this suggests
 7 that the similar results are driven by confounding from sun exposure.

8 This type of confounding is exactly what the authors found: in several studies, there was
 9 an association between PDE5 inhibitor use and basal cell carcinoma, with estimated risk ratios
 10 similar to those seen with melanoma. (Loeb, JX 93, at 2451, 2453, eTbl. 3 [relative risk of 1.21
 11 for melanoma and 1.19 and 1.18 for basal cell carcinoma (sildenafil and vardenafil or tadalafil),
 12 respectively]; Matthews, JX 94, at 1, 8, Tbl. 2 [1.14 and 1.15, respectively]; Shkolyar, JX 97, at
 13 985, Tbl. 2, [1.04 and 1.04, respectively].) The Matthews study also observed a statistical
 14 association between PDE5 inhibitor use and solar keratosis, another skin condition caused by sun
 15 damage. (Matthews, JX 94, at 2, 8, Tbl. 2.) In fact, the Matthews authors showed that men with
 16 solar keratosis were more likely to use PDE5 inhibitors *in the future* – in other words, that men
 17 who take PDE5 inhibitors have more long-term, chronic sun damage even before they take the
 18 medication than men who do not take PDE5 inhibitors. (*Id.* at 11.) As the Matthews study
 19 explained:

20 It is likely that the small observed increase in the risk of malignant
 21 melanoma among PDE5 inhibitor users is explained by higher sun
 22 exposure among PDE5 inhibitor users; this is strongly suggested
 23 by the increased risk of other diseases related to sun exposure
 24 among PDE5 inhibitor users and by the strong association between
 25 solar keratosis and subsequent PDE5 inhibitor use, which implies
 26 that men with high sun exposure were more likely to become
 27 PDE5 inhibitor users.

28 ⁷ Plaintiffs' experts agree that basal cell carcinoma, for example, is caused by sun damage and is not linked to PDE5 inhibitor use. (*See, e.g.,* Singh Tr., JX 54, at 89:11-16; Ahmed Tr., JX 65, at 189:5-12.)

1 (*Id.* at 3.)

2 The researchers also found that men who took PDE5 inhibitors differed from non-users in
 3 other ways that could confound or bias the results. For example, men who took PDE5 inhibitors
 4 had more interactions with the healthcare system, which could result in earlier melanoma
 5 detection. (Pottgard, JX 96, at 898-9.) In the Loeb study, PDE5 inhibitor users were younger,
 6 had fewer comorbidities, were more often married, had a higher educational level, and had a
 7 higher income than men who did not use PDE5 inhibitors. (Loeb, JX 93, at 2451.) It is believed
 8 that married men are more likely to be diagnosed with melanoma than unmarried men because
 9 married men have spouses who are more likely to observe suspicious lesions on their partners'
 10 skin, leading to earlier detection. (Liu-Smith Rep., JX 20, at 8; Liu-Smith Tr., JX 63, at 123:20-
 11 124:4.) Socioeconomic status also is a confounder, because men with a higher educational level
 12 and/or a higher income tend to have more interactions with doctors and other health care
 13 providers, also potentially resulting in earlier melanoma detection. (Jiang et al., BR J DERMATOL.
 14 2015;172:885-915, DX 38, at 887-91.)

15 As these newer observational studies were published, other researchers, to further evaluate
 16 the issue, began to combine the observational studies together in a single analysis, referred to as
 17 "meta-analysis." Meta-analysis is a method for pooling the results of multiple studies to increase
 18 overall sample size and reduce random error. (REF. MAN. at 579.) A meta-analysis arrives at a
 19 single risk estimate and helps reduce the risk that researchers will place undue emphasis or weight
 20 on any single study. (Ahmed Tr., JX 65, at 340:16-21.) Notably, however, confounding and bias
 21 in the underlying observational studies are not eliminated by combining them in a meta-analysis.
 22 (Singh Tr., JX 54, at 262:19-263:5.) Six sets of researchers published meta-analyses of the
 23 observational studies discussed above, in six separate journals. They all reported the same result
 24 with respect to melanoma: a small, statistical association similar to the majority of the underlying
 25 studies (risk ratios of 1.12 or 1.13), all of which were *smaller* than the associations seen for basal
 26 cell carcinoma, which nobody believes is biologically related to taking PDE5 inhibitors. (*See*
 27 App. Table 4.) Because of the confounding and detection biases noted above, and consistent with
 28

1 the conclusions of the underlying study authors, none of the authors concluded that the association
2 was causal.⁸

3 Tellingly, after one of the meta-analyses was published, the authors of four of the then-
4 published observational studies took the unusual step of submitting a joint letter explaining that
5 the small associations observed in some of the studies and in the meta-analyses were “unlikely to
6 be casual.” (Pottgard et al., PubMed Commons, Aug. 22, 2017, JX 95.) They explained that “all
7 the studies included analyses that probed [Bradford] Hill’s criteria for causality, and the findings
8 of all four studies suggested the association was unlikely to be causal.” (*Id.* at 3.)

9 **G. In 2016, The Dhayade Study Suggested A Biological Link Between PDE5**
10 **Inhibitors And Melanoma Progression, But A Subsequent Study Did Not**
11 **Confirm That Link.**

12 In 2016, after most of the observational studies were published but before any of the meta-
13 analyses appeared, researchers in Germany published the Dhayade study. (Dhayade et al., CELL
14 REP. 2016;14(11):2599-610, JX 87.) The Dhayade study did not attempt to replicate the
15 Arozarena study, which reported finding increased “invasion” in a single *in vitro* cell line.
16 Instead, the Dhayade study proposed that PDE5 inhibition results in increased melanoma cell
17
18

19 ⁸ (Loeb et al., J NATL CANCER INST. 2017;109(8), JX 92, at 109 “[A]lthough this meta-analysis
20 found a statistically significant association between PDE5 [inhibitors] and melanoma, it did not
21 satisfy Hill’s criteria for causality.”); Wang et al., ONCOTARGET 2017;8(28):46461-67, JX 99, at
22 46464-65 [“We cannot draw a conclusion that PDE5 inhibitor itself or other unmeasured or
23 uncontrolled confounders, especially sun exposure, are the cause of the increased malignant
24 melanoma, because weakness inherent in observational studies is that they may be subjected to
25 confounding.”]; Tang et al., J AM ACAD DERMATOL. 2017;77(3):480-88, JX 98, at 487 [“The
26 causality remains elusive, and further well-conducted large-scale prospective studies or
27 randomized trials are still needed to confirm our findings.”]; Han et al., ONCO TARGETS THER.
28 2018;11:711-20, JX 89, at 718 [“[A]t present, we could not determine whether the association
between PDE5i use and melanoma is causative.”]; Feng et al., MEDICINE 2018;97:e9601, JX 88, at
6 [“The results of the present analysis indicated that the association between PDE5 inhibitors and
melanoma risk might not be causal.”]; Deng et al., NEOPLASMA 2018;65(2):216-21, JX 86, at 220
[“[I]t is difficult for us to make a solid conclusion that application of PDE5 [inhibitors] could
cause the increased risk of melanoma directly.”].)

1 growth (not invasion) *in vitro* and increased tumor growth in mice. The Dhayade study never has
2 been replicated,⁹ and it has many significant methodological limitations.

3 First, unlike the Arozarena study, which tested human melanoma cells, the majority of the
4 experiments in the Dhayade study involved a type of mouse melanoma cells called B16 cells. (*Id.*)
5 Plaintiffs' experts agree that B16 mouse cells are not representative of most human melanomas,
6 since they lack BRAF or NRAS mutations, which are present in more than 75% of all human
7 melanomas. (Piazza Tr., JX 60, at 57:3-18; Ganesan Tr., JX 56, at 151:9-20.) Indeed, the
8 Dhayade study authors acknowledged that the pathway they studied in B16 mice "is probably not
9 universally conserved in all human melanomas." (Dhayade, JX 87, at 2604; Feil, MOLECULAR &
10 CELLULAR ONCOLOGY, 2017;4(5):e1188874, JX 104, at 1 ["Do all melanoma cells express the
11 growth-promoting cGMP pathway? Apparently not!"].)

12 Second, unlike the Arozarena study, the Dhayade authors did not analyze the impact of
13 PDE5 inhibitors alone in any *in vitro* experiment. (Dhayade, JX 87, at 2605-07.) Instead, the
14 Dhayade authors treated the B16 mouse cells with Viagra in combination with another substance
15 called c-type natriuretic peptide ("CNP"). CNP itself – without any contribution from a PDE5
16 inhibitor – caused precisely the same outcomes the Dhayade study attributed to PDE5 inhibitors,
17 including increased melanoma growth and increased cGMP signaling. (*Id.* at 2605, Figs. 6A-C.)
18 As a result, Plaintiffs' experts agree that it is not possible to know if Viagra alone would have the
19 same effects. (Ganesan Tr., JX 56, at 36:12-24; Haq Tr., JX 58, at 189:20-190:16.) Not only did
20 the Dhayade study never measure the effect of PDE5 inhibitors *in vitro* without CNP, but the
21 study authors conceded that it still "needs to be established in future studies" whether CNP is
22 present in human melanoma cells at all. (Dhayade, JX 87, at Fig. S5.) One of Plaintiffs' experts
23

24 ⁹ In fact, several other studies found – contrary to the Dhayade study – that PDE5 inhibitors either
25 significantly decreased or had no effect on the growth of melanoma cells. (*See* Zhang et al., J
26 CELLULAR BIOCHEM. 2012;113:2738-43, JX 118, Fig. 1B [mouse melanoma cells] & Suppl. Fig. B
27 [human melanoma cells]; Murata et al., ANTICANCER RES. 2010;30:355-58, JX 112, Fig. 3A & 3B
28 [human melanoma cells]; Drees et al., CANCER RES. 1993;53:3058-61, DX 39, Fig. 6 [mouse
melanoma cells].)

acknowledges that the authors merely “speculat[ed] on what the source of CNP could be.”
(Ganesan Tr., JX 56, at 37:14-22.)

Third, the *in vivo* mouse experiment in the Dhayade study used astronomically high daily doses of Viagra. The mice were given 200 mg/kg of Viagra daily in their drinking water for about two weeks. (Dhayade, JX 87, at 2605, Fig. 6F.) In comparison, the mice in the Arozarena study were given a 1.3 mg/kg daily dose, roughly the equivalent of an average-sized man taking the maximum daily dose of Viagra. (Arozarena, JX 85, at 54-55, Fig. 7K.) Thus, on a body weight basis, the dose used in the Dhayade study was more than 180 times the maximum human dose (Marais Rep., JX 27, at 43), dispensed every day, over the course of the two-week study. (Bastian Tr., JX 77, at 169:2-18.) Plaintiffs’ expert Dr. Piazza asserts that the difference is not truly that great, but even he admits that by his own calculations, the mice in the Dhayade study received 10 to 15 times the maximum daily human dose, continuously, for two weeks. (Piazza Tr., JX 60, at 209:17-210:7; Nair & Jacob, J BASIC & CLIN. PHARMA. 2016;7:27-31, DX 40.) The Dhayade authors accordingly admitted that “it is not clear whether the sildenafil concentration used in our experiments is also reached in patients.” (Dhayade, JX 87, at 2607.) Even using such massive doses, the Dhayade study showed only a small increase in tumor volume in mice treated with Viagra compared to the control group. (*Id.* at 2605, Fig. 6F.)

In 2018, different researchers tested in humans the hypothesis raised in the Dhayade study. They examined tissue samples from 470 melanoma patients and evaluated whether there was a difference in survival among the patients whose tissue samples could be affected by the PDE5-related signaling pathway hypothesized in the Dhayade study. (Wang et al., WORLD J MEN’S HEALTH 2018;36:e36, DX 41, at 3.) The researchers found no association. (*Id.* at 3-4, 8.) On that basis, they concluded “there is no strong molecular rationale” linking PDE5 inhibitor use to melanoma progression in humans. (*Id.* at 8.)

H. Since The Publication Of The Li Study, Regulators Have Analyzed Repeatedly The Scientific Evidence And Have Not Found A Causal Relationship.

In 2014 and 2016, following publication of the Li study, EMA’s Pharmacovigilance Risk Assessment Committee (“PRAC”) formally assessed the hypothesized link between PDE5

1 inhibitors and melanoma. PRAC received clinical trial and other data from Pfizer and Lilly, and it
 2 agreed with the companies' analyses that there was insufficient evidence to support a causal
 3 relationship between Viagra or Cialis use and melanoma.¹⁰ It found that the Li study had "several
 4 important limitations, including possible residual confounding, limited exposure assessment, and
 5 insufficient data for a meaningful study." (Preliminary PRAC Rapporteur Assessment Report on
 6 the Signal of Melanoma with Sildenafil, October 13, 2014, DX 43, at 7.) It also determined that
 7 the Arozarena study was "of little importance in human subjects" and that "[n]o plausible
 8 biological mechanism is available." (*Id.* at 12, 18.) The clinical studies also did "not indicate that
 9 there is an increased risk." (*Id.* at 19.) Accordingly, PRAC agreed with Pfizer that "there is no
 10 data to indicate, or support a causal role for sildenafil on an increased risk for melanoma." (*Id.*)
 11 PRAC similarly advised Lilly that it "agreed that currently there is no evidence of a causal
 12 association between tadalafil exposure and prostate cancer, bladder cancer, melanoma, skin
 13 cancer, and non-melanoma skin cancers." (European Medicines Agency PRAC PSUR
 14 Assessment Report, Active Substance Tadalafil, June 11, 2015, DX 44, at 6.) In 2017, following a
 15 review of the companies' updated analyses, a comprehensive assessment of the epidemiology, and
 16 an analysis of the Arozarena and Dhayade studies, PRAC reiterated that it "agree[d] with [Lilly's]
 17 proposal to close the signal at this stage. No change in the product information or the [Risk
 18 Management Plans] are warranted regarding melanoma." (European Medicines Agency PRAC
 19 PSUR Assessment Report, Active Substance Tadalafil, June 9, 2017, DX 45, at 33.)

20 Internal FDA analyses reached similar conclusions. In March 2015, FDA conducted its
 21 own evaluation of the Li study and determined that the study's findings were "insufficient for
 22 regulatory action due to the study's modest effect size and methodological limitations." (FDA
 23 Division of Epidemiology, Review of Published Study Report, Mar. 4, 2015, DX 46, at 2.)
 24 According to FDA, the methodological limitations of the Li study included its "crude and self-

25
 26 ¹⁰ (See Pfizer Response to PRAC Request, DX 5, at 10-23, 26-38, 42-43; Pfizer Response to June
 27 03, 2016 FDA Information Request, DX 42, at 3, 8, 56-57; Lilly 2016 Safety Topic Report, DX
 28 13, at 4-7, 69-70.)

1 reported measurement of drug exposure, relatively small sample size and possible residual
2 confounding.” (*Id.* at 12.) Regarding potential confounders, FDA noted that “[i]ndividual
3 exposure to UVR [ultraviolet radiation] is challenging to measure for cancer epidemiology studies
4 due to long latency periods between first exposure and diagnosis of cancer. Some of the proxies
5 for UVR measurement in the [Li] study, e.g., retrospective sun exposure history in high school and
6 number of blistering sunburns, may have poor to moderate reproducibility due to self-reported
7 exposure measurement for a long latency outcome.” (*Id.* at 12.) Like the Li study authors, FDA
8 emphasized that additional studies were needed “to strengthen the evidence with independent
9 replication of the findings in studies that better capture sildenafil use, and are able to measure dose
10 and duration.” (*Id.* at 2.) FDA did not recommend any warnings relating to melanoma or
11 conclude that the safety profile of the medications had changed. (*Id.*)

12 As researchers published additional studies, FDA continued to evaluate them and assess
13 the safety of Viagra and Cialis. In April 2016, FDA analyzed the Loeb study and an abstract of
14 the Lian study. (FDA Division of Epidemiology, Literature Review On The Association Between
15 [PDE5] Inhibitors and Risk of Malignant Melanoma, Apr. 27, 2016, DX 47, at 3, 5.) FDA found
16 that the Loeb study “was well conducted” and did “not support a causal relationship due to [the]
17 failure to demonstrate a dose-response relationship, lack of consistency in estimates for drugs from
18 the same therapeutic class, residual confounding, detection bias, insufficient epidemiological data
19 to support [a] biologically plausible mechanism; and low statistical power in some subgroup
20 analyses (e.g., advanced melanoma).” (*Id.*) FDA reaffirmed that “the epidemiologic studies to
21 date have not provided sufficient evidence to support an increased risk for melanoma with PDE5
22 inhibitors” and “recommend[ed] no regulatory action.” (*Id.*)

23 Three months later, after observing an increase in adverse event reports of melanoma with
24 PDE5 inhibitor use consisting almost entirely of the lawsuits filed by plaintiffs in this litigation –
25 the Agency requested adverse event data and analyses from Pfizer and Lilly. In reviewing the
26 adverse event data and the companies’ analyses, FDA was “unable to draw any causal inference
27 from this analysis” due to the “intermittent (and therefore inconsistent) exposure of PDE5
28 inhibitors in the treatment of ED, the long onset latency of melanoma, and insufficient data

1 quality” of the adverse event reports. (FDA Division of Pharmacovigilance II, Melanoma and
 2 PDE5 Inhibitors, Aug. 19, 2016, DX 48, at 11.)

3 **I. The Medical Community Never Has Concluded That PDE5 Inhibitors Cause**
 4 **Melanoma Progression; In Fact, Researchers Continue To Study Viagra And**
 5 **Cialis As Possible Treatments For Melanoma and Other Cancers.**

6 As the body of scientific evidence has continued to grow, no medical or scientific
 7 organization has concluded that PDE5 inhibitors cause melanoma or contribute to its
 8 “progression.” Leading organizations in the field – such as the National Cancer Institute,
 9 American Cancer Society, Melanoma Research Foundation, Skin Cancer Foundation, American
 10 Academy of Dermatology, American Society of Clinical Oncology, and American Urological
 11 Association – have not identified PDE5 inhibitor use as a risk factor for melanoma or advised
 12 patients with melanoma or at risk for melanoma to stop taking the medications. Public health
 13 agencies, such as the Centers for Disease Control and Prevention and the International Agency for
 14 Research on Cancer (“IARC”), a division of the World Health Organization, also have not issued
 15 any new recommendations. Indeed, as recently as April 2018, the American Academy of
 16 Dermatology informed its more than 20,000 members that “[r]esearch has not proven a causal
 17 relationship between the use of erectile dysfunction drugs and skin cancer risk.” (AAD, Practice
 18 Management Center, *Erectile dysfunction drugs and skin cancer*, Apr. 16, 2018, DX 49.)

19 To the contrary, in the medical and scientific world – outside of this litigation – researchers
 20 have focused their efforts on studying the use of PDE5 inhibitors to prevent and treat cancers,
 21 including melanoma. The results of three clinical trials published since 2015 indicate that
 22 treatment with Cialis together with other compounds reduces the number of myeloid-derived
 23 suppressor cells, which tumors use to suppress the immune system, in head and neck squamous
 24 cell carcinoma and metastatic melanoma. (Weed et al., CLIN CANCER RES. 2015;21(1):39-48, DX
 25 50; Califano et al., CLIN CANCER RES. 2015;21(1):30-38, DX 51; Hassel et al.,
 26 ONCOIMMUNOLOGY 2017;6(9):e1326440, JX 105.) The most recent of these clinical trials, the
 27 Hassel study, investigated whether daily use of Cialis combined with another medication would be
 28 beneficial for patients with metastatic melanoma. (Hassel, JX 105, at e1326440.) Based on the
 positive results in some patients, the study authors concluded that PDE5 inhibitors in combination

1 with other medications may be “a potential new treatment option for patients with metastatic
2 melanoma.” (*Id.* at e1326440-7.)

3 Today, there are at least 11 ongoing clinical trials investigating PDE5 inhibitors as
4 potential treatments for cancer. (Pantziarka et al., ECANCER 2018;12:824, DX 52, at 9-11, Tbl. 4.)
5 Plaintiffs’ experts agree it would be unethical to conduct these trials – and expose cancer patients
6 to PDE5 inhibitors – if it were accepted within the medical community that PDE5 inhibitors can
7 cause melanoma progression. (Singh Rep., JX 2, at 10; Ahmed Tr., JX 65, at 194:2-13.)

8 **II. PLAINTIFFS’ EXPERTS AND THEIR UNRELIABLE METHODS**

9 Plaintiffs proffer six experts, who offer varying opinions, but generally point to the same
10 body of evidence in support of those opinions: (1) three epidemiologists who focus primarily on
11 the clinical data (Drs. Sonal Singh, Feng Liu-Smith, and Rehana Ahmed-Saucedo) but also offer
12 biological plausibility opinions; and (2) three scientists who focus primarily (or solely) on the
13 preclinical data (Drs. Gary Piazza, Anand Ganesan, and Rizwan Haq).¹¹

14 **A. Dr. Sonal Singh**

15 **1. Background**

16 Dr. Singh is a medical doctor who holds a master’s degree in public health. He is an
17 Associate Professor of Medicine at the University of Massachusetts, where he treats patients two
18 days a week in internal medicine. (Singh Rep., JX 2, at 3-4; Singh Tr., JX 54, at 7:16-25; 15:19-
19 23.) He is neither a dermatologist nor an oncologist; he sees very few patients with melanoma;
20 and he never has performed research relating to melanoma. (Singh Tr., JX 54, at 12:12-17, 17:21-
21 25, 32:5-7, 130:3-5.) Dr. Singh is not a melanoma expert, and his testimony reflects his lack of
22 understanding of melanoma biology. (*See, e.g., id.* at 130:3-132:9 [“Q. What types of biological
23 changes take place in a human between the time that a melanoma process begins and the time of

24 ¹¹ Plaintiffs designated two experts – Drs. Ahmed and Piazza – as offering opinions against both
25 Pfizer and Lilly. They designated two experts – Drs. Singh and Haq – as offering opinions against
26 Pfizer only, and they designated two experts – Drs. Liu-Smith and Ganesan – as offering opinions
27 against Lilly only. (*See* Ahmed Viagra Rep., JX 13; Ahmed Cialis Rep., JX 14; Piazza Rep., JX 5;
28 Singh Rep., JX 2; Haq Rep., JX 9; Liu-Smith Rep., JX 20; Ganesan Rep. JX 17.) Dr. Ahmed-
Saucedo prefers to be referred to as Dr. Ahmed. (Ahmed Tr., JX 65, at 8:20-22.)

1 diagnosis? A. . . . I just don't think that's my area of expertise."]; *id.* at 46:22-47:1 ["Q. On
2 average, how long does it take for a melanoma to develop? A. Years. Q. Can you be more
3 specific? A. I can't. I don't know."].)

4 Dr. Singh testifies frequently as an expert for plaintiffs. Multiple courts have excluded his
5 opinions under *Daubert* where he concluded that a causal relationship between a medication and a
6 disease existed without sufficient data to support his opinion.¹²

7 2. Opinions Offered

8 Dr. Singh offers opinions about Viagra only. (Singh Rep., JX 2, at 1.) He opines that
9 Viagra can cause melanoma invasion, but *not* growth (Singh Tr., JX 54, at 55:21-56:5), and that a
10 single Viagra pill is sufficient to cause melanoma invasion, but he cannot say by how much or
11 over what time frame. (*Id.* at 115:7-25; 117:3-6.) Dr. Singh continues to prescribe PDE5
12 inhibitors to his patients, and over the past year (after he was retained by Plaintiffs' counsel) he
13 prescribed the medications "10, 20 times, something more," without regard to whether these
14 patients had melanoma. (*Id.* at 12:18-13:9; 18:7-17; 20:1-11.) Dr. Singh considers himself to be a
15 "public health scientist," but has neither published his opinions in the peer-reviewed literature nor
16 expressed them to anyone in the medical, scientific, or regulatory communities. (*Id.* at 28:14-17;
17 28:23-29:4; 29:25-30:18 [stating he has "concerns" based on the results of his analysis, but he
18 never has "expressed those concerns"].)

19 3. Dr. Singh's Flawed Methodology

20 Dr. Singh bases his causation opinion on a "statistically significant increased risk of
21 malignant melanoma in most of [the] observational studies (5/6) and six independent meta-
22 analysis." (Singh Rep., JX 2, at 1.) At his deposition, however, he conceded that only three of the
23

24 ¹² See *McWilliams v. Novartis AG*, No. 2:17-CV-14302, 2018 WL 3364608, at *2-5 (S.D. Fla. July
25 9, 2018) (partially excluding Dr. Singh's opinion that Tasigna is causally associated with
26 atherosclerosis characterized as "severe" or "rapidly progressive"); *In re Lipitor (Atorvastatin
27 Calcium) Mktg., Sales Practices & Prods. Liab. Litig.*, 174 F. Supp. 3d 911, 921-927 (D.S.C.
28 2016) (partially excluding Dr. Singh's general causation opinion regarding all but the highest dose
of Lipitor where data were insufficient to claim causation); *aff'd*, 892 F.3d 624, 640-642 (4th Cir.
2018) (affirming partial exclusion of Dr. Singh's general causation opinion).

1 six observational studies then published offer results in their primary analyses that are statistically
 2 significant, and he acknowledged that the authors of all the studies concluded that their results do
 3 not support a finding of causation. (*See* Singh Tr., JX 54, at 252:25-253:4 [agreeing that only
 4 three of the observational studies’ primary results were statistically significant]; *id.* at 82:3-83:13
 5 [stating that “obviously they [the published study authors] have opined that it is not a causal”
 6 relationship].)

7 Dr. Singh agrees that it is “very important” to consider both “bias and confounding in the
 8 interpretation of data from observational studies” (*id.* at 65:20-24), but he did not do so reliably
 9 when evaluating the Li study. Dr. Singh admits that the measure of prior sun exposure used in the
 10 Li study was “crude”; he cannot rule out the possibility that the Li study risk estimate was higher
 11 than all other studies due to the possibility of confounding; and he “possibly” agrees with the Li
 12 study authors that possible differences in health status and lifestyle practices between Viagra users
 13 and non-users may have confounded their findings. (*Id.* at 171:15-172:9; 181:12-24; 183:8-
 14 184:5.) When asked to explain why some studies found statistical associations between PDE5
 15 inhibitor use and non-melanoma skin cancers (which suggests that the observed association with
 16 melanoma is likely the result of confounding by sun exposure), Dr. Singh suggested that basal cell
 17 carcinoma and squamous cell carcinoma are associated with “a different kind of sun exposure.
 18 Cumulative sun exposure.” (*Id.* at 89:11-16.) Not only is this explanation contradicted by
 19 Plaintiffs’ melanoma experts,¹³ but Dr. Singh also admitted that “how Viagra impacts basal cell
 20 carcinoma is really not . . . my area of expertise, and not something that, you know, I’ve looked
 21 at.” (*Id.* at 177:18-178:7.)

22 Dr. Singh takes positions in this litigation that are contrary to his testimony in prior cases.
 23 Dr. Singh agrees that it is important to consider how regulators and medical organizations have
 24 evaluated a potential association when analyzing the possibility of a causal relationship and has

25 ¹³ For example, Dr. Ganesan states in his report that “melanomas can develop after long term UV
 26 exposure while others can develop from moles (pre-cancers) after short bursts of UV exposure.”
 27 (Ganesan Rep., JX 17, at 11.) Similarly, Dr. Haq testified that “UV exposure in general is
 28 associated with a higher risk of melanoma.” (Haq Tr., JX 58, at 229:23-230:11.)

1 done so in his prior litigation work. (*Id.* at 200:12-21 [“I think it’s important to consider what
 2 regulators have been thinking about this particular association.”]; Singh Initial Lipitor Rep., DX
 3 53, at 6 [“I also searched for existing guidelines from the American Diabetes Association,
 4 American Heart Association, . . . American College of Cardiology on their interpretation of the
 5 evidence on statins and the risk of diabetes.”]; Singh Lipitor Supp. Rep., DX 54, at 10-25
 6 [analyzing multiple FDA regulatory submissions as part of causation assessment].) Here, Dr.
 7 Singh ignores EMA’s and FDA’s assessments; he did not describe them at all in his report (*see*
 8 Singh Rep., JX 2, *passim*); and he did not even review FDA’s assessment until a few days before
 9 his deposition. (Singh Tr., JX 54, at 198:3-20.) Nor could Dr. Singh recall reviewing guidelines
 10 or analyses by any of the relevant medical organizations. (*Id.* at 197:5-198:2, 199:21-200:10.)

11 Dr. Singh’s emphasis on a single observational study result, the Li result, is at odds with
 12 his prior methodology to assess causality. Dr. Singh agrees that any causality opinion should be
 13 based on the totality of available evidence; that a single study rarely, if ever, establishes a causal
 14 relationship; and that it is methodologically improper to cherry-pick individual studies to fit a
 15 desired result. (*Id.* at 42:23-43:8, 201:10-24.) He regularly relies on meta-analyses to assess
 16 causal relationships between medications and diseases, including cancer; indeed, he has asserted
 17 repeatedly that meta-analyses are more reliable to evaluate causality than individual observational
 18 studies.¹⁴ In his prior litigation work, Dr. Singh also has relied on clinical trial data (including
 19 unpublished data and company summaries of these data) as a basis for his causation

21 ¹⁴ (*See* Singh Rep., JX 2, at 6-8 [citing prior meta-analyses and systematic reviews]; *id.* at 8 [citing
 22 Turner et al., BR. J. CLIN. PHARMACOL. 2014;78(2):258-73, DX 55]; Singh Initial Lipitor Rep., DX
 23 53, at 5 [“Short of a [sic] definitive randomized clinical trial data on the outcome of interest,
 24 causal inference must be drawn from robust meta-analysis of controlled trials or observational
 25 studies.”]; *id.* at 41 [citing his meta-analysis as a basis for finding causation]; Singh Lipitor Tr.,
 26 DX 56, at 428:5-8 [“I’m a meta-researcher. I do meta-analysis... I am one of the most productive
 27 meta-analysts.”]; Singh Rep. in *Lauris v. Novartis AG*, No. 1:16-cv-00393-SHE (E.D. Cal.), Dkt.
 28 No. 112-1, DX 57, at 5-6 [“Systematic reviews (with homogeneity defined as free of variations in
 the direction and degree of results between individual results) and meta-analysis of randomized
 controlled trials are considered the highest level of evidence (Level 1a) when evaluating the effect
 of interventions.”]; Singh Rep. in *McWilliams v. Novartis AG*, No. 2:17-cv-14302 (S.D. Fla.), Dkt.
 No. 56-3, DX 58, at 6 [same].)

1 opinions. (*See* Singh Initial Lipitor Rep., DX 53, at 5-6, 9-15; Singh Lipitor Supp. Rep., DX 54 at
2 2-7, 10-28; Singh Rep. in *Lauris v. Novartis AG*, DX 57, at 5-6; Singh Rep. in *McWilliams v.*
3 *Novartis AG*, DX 58, at 5-7.)

4 But Dr. Singh did not employ the same methodology here. He did not review – or even
5 search for – Pfizer’s clinical trial data prior to forming his opinion and submitting his report in this
6 litigation, much less include them in a meta-analysis. (Singh Rep., JX 2, at 48; Singh Tr., JX 54,
7 at 40:17-21, 257:3-258:10.) Indeed, he asserts that the Viagra clinical trial data were “not a
8 necessary part” of his analysis. (*Id.* at 258:23-259:21.) Instead, in reaching his causality opinion,
9 he favors the results of a single observational study over both the randomized clinical trial data
10 and a number of meta-analyses that were designed to synthesize the totality of available
11 observational studies. (*See* Singh Rep., JX 2, at 3 [citing Li study as most reliable estimate for
12 magnitude of effect]; *id.* at 44 [identifying Li study risk estimate in evaluating strength of
13 association for Bradford Hill causality assessment]; Singh Tr., JX 54, at 169:4-170:5 [stating that
14 the Li study “provides a strong weight in support of a causal association”].)

15 Finally, in his prior litigation work, Dr. Singh noted that the Bradford Hill criteria are
16 “ordered . . . sequentially, from most important to least, in regards to causal inference[.]” with the
17 most important criteria being strength of association, consistency, specificity, temporality, and
18 dose response, and the least important factor being analogy. (Singh Initial Lipitor Rep., DX 53, at
19 32.) Here, Dr. Singh reshapes his approach to the Bradford Hill criteria in a results-oriented
20 fashion. He does not weigh or rank the Bradford Hill criteria or explain their relative contribution
21 in reaching his causation opinion. And by his own admission, three of the five criteria Dr. Singh
22 generally deems “most important” are not met: the association observed in the Li study is “weak”
23 (Singh Tr., JX 54, at 106:12-16); there is no evidence of a dose-response relationship (Singh Rep.,
24 JX 2, at 46 [“In the present scenario, we do not have evidence of a dose-response gradient because
25 of the challenges in measuring exposure across studies with a drug used on an as-needed basis.”];
26
27
28

1 Singh Tr., JX 54, at 268:8-269:16, 270:11-271:10, 287:13-20);¹⁵ and specificity is absent because
 2 melanoma has multiple causes and is not specific to exposure to Viagra. (Singh Rep., JX 2, at 45.)

3 Dr. Singh also asserts that the Arozarena and Dhayade studies provide evidence of
 4 biological plausibility. (Singh Rep., JX 2, at 47.) Yet Dr. Singh could not answer basic questions
 5 about the design of these studies and disclaimed any expertise in melanoma biology. (*See, e.g.*,
 6 Singh Tr., JX 54, at 131:17-22 [“I’m not posing as a melanoma expert in, you know, the
 7 mechanics of melanoma development.”]; *id.* at 140:7-14 [“Q. . . . Did Dr. Dhayade conduct any in
 8 vitro experiments involving Viagra alone? A. I mean, this is really not my area of expertise, and I
 9 hate to answer the question.”].) Dr. Singh also agrees that Pfizer’s animal studies are
 10 methodologically “relevant to the assessment of carcinogenicity, and that’s why we do them.”
 11 (Singh Tr., JX 54, at 135:10-136:4.) Yet he did not “go into the details” of these studies as part of
 12 his analysis of biological plausibility, stating that such data are “not my area of expertise.” (*See*
 13 *id.* at 133:6-21.)

14 **B. Dr. Feng Liu-Smith**

15 **1. Background**

16 Dr. Feng Liu-Smith, a research scientist recently turned epidemiologist, is an Assistant
 17 Professor in Residence, a non-tenure track position at the University of California at Irvine. She
 18 offers opinions about Cialis only. (Liu-Smith Tr., JX 63, at 319:16-320:5.)

19 **2. Opinions Offered**

20 In her report, Dr. Liu-Smith offers a generalized opinion that Cialis can cause melanoma
 21 development. (Liu-Smith Rep., JX 20, at 4, 41.) At her deposition, she substantially amended that
 22 position, instead conditioning her opinions on whether the melanoma cells at issue have a BRAF
 23 mutation or not: for cells *without* a BRAF mutation, Dr. Liu-Smith said that PDE5 inhibitors can
 24

25 ¹⁵ In other litigations, Dr. Singh focused on the presence of a dose-response relationship to
 26 establish causation. (*See* Singh Rep. in *Lauris v. Novartis AG*, No. 1:16-cv-00393-SHE (E.D.
 27 Cal.), Dkt. No. 112-1, DX 57, at 18, 36 [noting that the “evidence suggests a dose-response effect,
 28 and further strengthens the inference of causality”]; Singh Rep. in *McWilliams v. Novartis AG*,
 No. 2:17-cv-14302 (S.D. Fla.), Dkt. No. 56-3, DX 58, at 18, 36.)

1 cause growth, but not stimulate invasion; in cells *with* a BRAF mutation, PDE5 inhibitors can
 2 cause invasion, but cannot cause growth. (Liu-Smith Tr., JX 63, at 62:10-63:11.) None of the
 3 observational studies at issue include data on BRAF mutation status, and no other expert has
 4 adopted this distinctive hypothesis – one that Dr. Liu-Smith admits conflicts with the views of her
 5 fellow experts. (*Id.* at 65:7-22, 66:11-24.)

6 **3. Dr. Liu-Smith’s Flawed Methodology**

7 Dr. Liu-Smith acknowledges that none of the observational studies upon which she rests
 8 her opinion reach the causation conclusion she offers. (*Id.* at 317:16-318:14.) She also
 9 acknowledges that observational studies typically are not “designed to determine [] cause and the
 10 effect” (*id.* at 74:8-75:4), and the studies here specifically were not designed to “[p]rove or
 11 disprove causation.” (*Id.* at 104:12-105:2.) Dr. Liu-Smith repeated this refrain throughout her
 12 deposition. (*See, e.g., id.* at 226:1-9 [“None of the epidemiology can prove cause and effect.
 13 That’s what I have been keeping saying. These epidemiology studies do not prove cause and
 14 effect.”].)

15 Dr. Liu-Smith claims that biological plausibility is necessary to prove causation, which is
 16 why, in her opinion, the authors of the observational studies do not find causation. (*Id.* at 104:12-
 17 105:8.) But she also acknowledges that no scientist outside of this litigation has concluded that a
 18 causal association exists even when taking biological plausibility into account. (*Id.* at 105:9-17
 19 [“Q. And, to be clear, you’re not aware of any scientist, whether published or unpublished, who
 20 has looked at the epidemiological studies and biological plausibility to conclude that the evidence
 21 supports a causal association; correct? A. I’m not aware of any scientist.”].) Indeed, she
 22 recognizes that a publication on her own university’s website rejects the notion that PDE5
 23 inhibitors have been shown to cause melanoma development. (*Id.* at 316:11-15 [“Q. So, at least
 24 as of December of ’16, Dr. Yafi at the University of California-Irvine medical department
 25 disagrees with the opinions you’re offering in this litigation; correct? A. Correct.”].) Even when
 26 the topic arose in her department, she stayed silent rather than subjecting her litigation views to the
 27 peer review of her colleagues. (*Id.* at 82:22-84:1 [“Q. [D]id you raise your hand in that meeting
 28 and say, I believe there is a causal association between PDE5 inhibitors and melanoma

1 development? A. No, I did not. It's what – we circulated a email about it. Q. And did you write
2 in that email, it's my view that there is a causal association between the use of PDE5 inhibitors
3 and melanoma development? A. This was not raised by me. It was raised by another doctor. Q.
4 Okay. Did the other doctor say, I believe there is a causal association between the use of PDE5
5 inhibitors and melanoma development? A. He's – I believe it's more like association. Did not
6 say causal.”].)

7 Dr. Liu-Smith's inability to articulate any reasoned basis for the positions she took in her
8 report is particularly striking. She resists recognizing even the basic epidemiological principle
9 (fully acknowledged by Dr. Singh) that the stronger the observed association, the greater the
10 likelihood of a true relationship. (*Id.* at 43:2-46:22; 134:24-135:20; 307:11-309:21; 311:16-21;
11 Singh Tr., JX 54, at 101:2-11.) When confronted with what she acknowledged to be the lack of
12 any dose-response relationship, she speculated that there is “something going on.” (*Id.* at 189:21-
13 190:13 [“I'm not suggesting any of these [potential dose-response relationships] – because I don't
14 have any data to base on my suggestion at all, but clearly there is something going on.”].)

15 Faced with multiple observational studies showing a similar small statistical association
16 between basal cell carcinoma and PDE5 inhibitor use, Dr. Liu-Smith dismissed using basal cell
17 carcinoma as a negative control because PDE5 inhibitors must in her view be causing the increase
18 in basal cell carcinoma — a new opinion that no other expert in this litigation (or anywhere in the
19 world) has ever expressed and one that misapprehends the basic epidemiological concept of a
20 negative control. (*Id.* at 114:10-20 [“Q. And you certainly understand that the various authors
21 who used basal-cell carcinoma as a negative control did so based on the hypothesis that basal-cell
22 carcinoma does not seem to be implicated by the PDE5 pathway; correct? A. Correct. That's
23 what – that's their assumption when they did the study. But the – like I said, science can prove
24 themselves wrong at a later time. So this is one of those occasions. It looks like basal-cell
25 carcinoma is actually associated with PDE5 inhibitor use.”].) By the end of her deposition, Dr.
26 Liu-Smith retracted that opinion – leaving her with no explanation for the finding of an association
27 with basal cell carcinoma. (*Id.* at 333:24-334:13 [“[M]aybe I shouldn't say this because this is
28 like very – not really based on the scientific evidence.”].)

1 Indeed, Dr. Liu-Smith's opinions were so jumbled that at the end of her deposition her
 2 counsel took the remarkable step of prompting her to disclaim her deposition testimony in favor of
 3 her report. (Liu-Smith Tr., JX 63, at 347:2-9 ["Q. Doctor, if you gave testimony today that is in
 4 conflict with the opinions you gave in your report, which would you want Judge Seeborg to rely
 5 on, your deposition or your report? THE WITNESS: I -- my report."].)

6 **C. Dr. Rehana Ahmed**

7 **1. Background**

8 Dr. Ahmed is a dermatologist in private practice and a non-tenure track Assistant Professor
 9 of Dermatology at the University of Minnesota, where she sees patients at the university clinic one
 10 to two days per month. (Ahmed Viagra Rep., JX 13, at 2-3; Ahmed Tr., JX 65, at 31:12-25.) She
 11 offers opinions about both Viagra and Cialis. In 2017, she co-authored a peer-reviewed article on
 12 risk factors for skin cancer in organ transplant recipients. Her study made no mention of PDE5
 13 inhibitor use as a potential risk factor for melanoma. (*Id.* at 61:25-62:10; Garrett et al., JAMA
 14 Dermatol. 2017;153(3):296-303, DX 59.) Although Dr. Ahmed is a member of the American
 15 Academy of Dermatology, she was unaware of the Academy's April 2018 statement rejecting a
 16 causal connection between PDE5 inhibitors and melanoma. (Ahmed Tr., JX 65, at 63:17-23;
 17 64:16-65:4.) Dr. Ahmed does not ask her patients about PDE5 inhibitor use; she does not recall
 18 ever having a conversation with any of them about PDE5 inhibitor use; and she has not changed
 19 her practice in treating or counseling patients since preparing her report in this case. (*Id.* at 35:10-
 20 25, 42:6-17, 43:3-8, 45:21-25, 46:1-17.)

21 **2. Opinions Offered**

22 Dr. Ahmed opines in her report that Viagra or Cialis use "increases the risk of
 23 development of melanoma in a vulnerable subset of patients." (Ahmed Cialis Rep., JX 14, at 3;
 24 Ahmed Viagra Rep., JX 13, at 3.) At her deposition, however, she would not say that PDE5
 25 inhibitors actually cause an increased risk of melanoma. (Ahmed Tr., JX 65, at 174:2-175:12.)
 26 Nor could she specify which patients are part of the so-called "vulnerable subset," which she
 27 admits is not something she can do using either epidemiology or her clinical background. (*Id.* at
 28 109:12-110:1; 364:6-18, 365:7-367:4.) Dr. Ahmed contends that a single dose of a PDE5

1 inhibitor, taken at any time in a patient's life before diagnosis, is sufficient to cause melanoma
 2 progression (*id.* at 115:18-116:6; 117:15-21), but she is not aware of any evidence that suggests
 3 that temporary inhibition of PDE5 by Viagra or Cialis in a cell can have a permanent effect. (*Id.*
 4 at 119:25-120:6.)

5 **3. Dr. Ahmed's Flawed Methodology**

6 Dr. Ahmed acknowledges that her opinions conflict with those of the study authors,
 7 medical organizations, and regulatory agencies who have analyzed whether there is a relationship
 8 between PDE5 inhibitor use and melanoma. (*Id.* at 65:23-66:25, 289:14-290:2.) She could not
 9 recall whether any published study author has concluded that PDE5 inhibitors cause melanoma
 10 and acknowledged, "I haven't looked at all the peer-reviewed literature. . . . I simply, in my report,
 11 talked about my views." (*Id.* at 400:7-14; 401:2-14.)

12 Dr. Ahmed conducted a cursory analysis of Pfizer's clinical trial data for Viagra,
 13 suggesting that those data showed Viagra increased the risk of melanoma by 62 percent. (Ahmed
 14 Viagra Rep., JX 13, at 28.) Yet, she withdrew that conclusion at her deposition, conceding that
 15 she "didn't perform a full analysis" in a manner consistent with what she would do if she were
 16 preparing a peer-reviewed publication and that she had already formed her causation opinion
 17 before examining the clinical trial data. (Ahmed Tr., JX 65, at 247:14-248:25, 250:25-251:9.)

18 Dr. Ahmed claims to have "applied the Bradford Hill criteria in formulating [her]
 19 opinions" in both her reports, but she neither lists nor analyzes any of the Bradford Hill criteria in
 20 her Cialis report and instead defers to Dr. Liu-Smith. (*See* Ahmed Cialis Rep., JX 14, at 12-13.)
 21 In her Viagra report, Dr. Ahmed does not weigh or rank the Bradford Hill criteria or explain their
 22 relative contribution in concluding a causal relationship exists – she merely dismisses missing or
 23 weak criteria and states that *none* of the criteria, except temporality, are necessary to conclude
 24 causation. (*See, e.g.,* Ahmed Viagra Rep., JX 13, at 18-19; Ahmed Tr., JX 65, at 383:21-384:5.)
 25 Regarding the first Bradford Hill factor – whether the associations reported in the observational
 26 studies are strong – Dr. Ahmed cherry-picks two subgroup analyses from the Li study. (Ahmed
 27 Viagra Rep., JX 13, at 17-18.) She fails to consider any of the primary risk estimates from the
 28 later observational studies or the six meta-analyses, all of which report much lower statistical

1 associations or no associations at all. (Ahmed Tr., JX 65, at 299:4-23, 361:16-362:6, 323:8-
2 324:12, 338:6-14.)

3 Nor does Dr. Ahmed reliably consider whether the observed associations are driven by
4 confounding or bias. She ignores the studies and meta-analyses that observed a statistically
5 significant association between basal cell carcinoma and PDE5 inhibitors. (*Id.* at 188:13-15 [“Q.
6 Do PDE5 inhibitors cause basal cell carcinoma? ... A. I haven’t studied that question at
7 length.”]; *id.* at 373:9-13 [“Q. In this part of your report, you do not cite the basal cell carcinoma
8 results from any meta-analysis of observational studies; correct? A. Actually, I guess I – I
9 haven’t put references here, so...”].) And while Dr. Ahmed points to certain subgroup analyses as
10 potentially suggesting a dose-response relationship, she admits that none of these selective
11 findings reaches the level of evidence required under the standard methodology she uses outside of
12 litigation to conclude that a dose-response relationship exists. (*See id.* at 196:4-9 [noting that Dr.
13 Ahmed conducts tests for trend to determine whether a dose-response effect exists in practice and
14 her own publications]; *id.* at 302:20-24, 313:8-314:4, 325:20-326:8 [noting that tests for trend
15 were not significant in the Pottgard, Matthews, and Lian studies].)

16 Dr. Ahmed also concludes that “plausible mechanisms of action exist” by which PDE5
17 inhibitors “increase[] the development and progression” of melanoma. (Ahmed Viagra Rep., JX
18 13, at 8-9.) She claimed that “all of the data that I looked at supports my theory [of biological
19 plausibility], whether or not it has a positive result or a negative result.” (Ahmed Tr., JX 65, at
20 140:25-141:2.) Yet Dr. Ahmed could not point to any particular cell or animal experiments in the
21 Arozarena or Dhayade studies that tended to support or refute her opinion. (*Id.* at 136:6-14,
22 156:16-157:8 [“So I don’t know that I could say definitively that doing one experiment shows this
23 and one experiment shows that.”].) Dr. Ahmed further admitted that cell experiments are “not
24 speaking towards the medication effect in a human on its own” (*Id.* at 85:8-86:1) and that in cell
25 studies, “the medication doesn’t pass through a similar type of degradation system or metabolism
26 system as it would in a human body.” (*Id.* at 125:10-23.) Dr. Ahmed accordingly was unwilling
27 to say that melanoma progression with PDE5 inhibitor exposure was probable in the doses
28 prescribed to humans, only that it was possible: “I don’t know that we know specifically how

1 doses translate from research in cell culture [and] mice to human doses, but I think it is possible.”

2 (*Id.* at 116:13-117:1.)

3 **D. Dr. Gary Piazza**

4 **1. Background**

5 Dr. Gary Piazza is a pharmacologist and professor at the University of South Alabama.
6 (Piazza Rep., JX 5, at 2-4.) As discussed above, for the past 25 years his work has focused on
7 development of pharmacologic treatments for various types of cancer. (*Id.*) He has applied for
8 and received patents on the use of PDE5 inhibitors for the *treatment* of cancer, published peer-
9 reviewed studies on his testing of those compounds, and received federal grants to support his
10 work.

11 **2. Opinions Offered**

12 In contrast to his prior research and publications, Dr. Piazza proposes to opine here that a
13 plausible biological mechanism exists by which PDE5 inhibitors can “enhance or accelerate the
14 growth or the invasiveness” of pre-existing melanoma cells. (Piazza Tr., JX 60, at 22:13-23:5.) In
15 other words, he proposes to opine that PDE5 inhibitors can have a *pro-cancer* effect – though he
16 “wouldn’t say [a PDE5 inhibitor] *causes* melanoma progression.” (*Id.* at 151:25-152:17
17 [emphasis added].) He contends that a single 25 milligram pill of Viagra (the lowest FDA-
18 approved dose) could accelerate melanoma progression. (Piazza Tr., JX 61, 378:8-379:17.) When
19 asked if there was any dose of the medication that could not do so, he stated, “I really don’t know”
20 and that even a single dose as low as “1 milligram or .1 milligram or .01 milligram” might have
21 this effect. (*Id.* at 379:18-381:3, 384:4-19.) When asked what studies in humans support this
22 single pill opinion, Dr. Piazza admitted, “I don’t think those studies have been done.” (*Id.* at
23 385:14-25.)

24 **3. Dr. Piazza’s Flawed Methodology**

25 Dr. Piazza agrees that many things can cause a melanoma cell to grow or invade (Piazza
26 Tr., JX 60, at 24:6-20), and that he has no way to tell whether a melanoma cell in a human has
27 grown or invaded due to exposure to a PDE5 inhibitor. (*Id.* at 33:16-24.) He cannot describe or
28 explain how much more quickly a melanoma cell will grow or invade when exposed to a PDE5

1 inhibitor. (Piazza Tr., JX 61, at 398:15-400:11.) For his opinions, Dr. Piazza primarily relies on
 2 the Arozarena and Dhayade studies, but he admittedly disagrees with many of the authors’
 3 conclusions (Piazza Tr., JX 60, at 139:7-146:11 [Arozarena], 199:9-200:8 [Dhayade]), as well as
 4 the conclusions of other peer-reviewed studies he cites. (*Id.* at 254:19-22, 256:2-257:21.)
 5 Because he offered deposition testimony that conflicted with his report, at the end of his
 6 deposition, Plaintiff’s counsel prompted Dr. Piazza to testify that his report is “more reliable” than
 7 his testimony and that the Court should rely on his report if there is any conflict with his
 8 testimony. (*See* Piazza Tr., JX 61, at 506:15-507:6.)

9 As discussed, Dr. Piazza’s litigation opinions are dramatically at odds with his own
 10 publications and research regarding PDE5 inhibitors. He has more than 20 years of studies and
 11 publications reporting that PDE5 inhibitors may be effective alone or in combination with other
 12 anti-cancer medications to treat melanoma and other cancers. (*See* Zhu et al., ONCOTARGET
 13 2017;8(41):69264-69280, JX 119; Whitt et al, J BIOMED RES. 2016;30(2):120-133, DX 60; Piazza,
 14 CANCER PREV RES. 2017;10(7):373-376, DX 61; US Patent Application No. US 20160143912 A1
 15 and U.S. Patent No. 10,039,764 B2, DX 62; US Patent No. 9,365,528 B2, DX 63; El-Sharkawy et
 16 al., ARCH PHARM. 2018;351(5):e1800018, DX 64; US Patent No. 5,858,694, DX 18; US Patent
 17 No. 6,156,528, DX 65; Tinsley et al., CANCER PREV RES 2011;4(8):1275-84, DX 66; US Patent
 18 No. 9,388,139 B2, DX 67; Ahmed et al., EUR J MED CHEM. 2012;57:329-43, DX 68; Gurpinar et
 19 al., FRONT ONCOL. 2013;3;181, DX 69; Piazza Grant for PDE5 Inhibitor for Breast Cancer
 20 Chemoprevention, National Cancer Institute, Division of Cancer Prevention, Grant
 21 R01CA155638, DX 70.) In June 2017 – months after he had been retained by Plaintiffs in this
 22 case – Dr. Piazza published a peer-reviewed editorial entitled “Validation of PDE5 as a
 23 Chemoprevention Target,” in which he commented favorably on a recent study finding that Viagra
 24 can suppress colorectal cancer in mice, described his own prior findings that PDE5 inhibitors can
 25 be used to kill colorectal cancer cells, and advocated for human clinical trials of Viagra in
 26 combination with another PDE5 inhibitor to treat colorectal cancer. (*See* Piazza, DX 61; Piazza
 27 Tr., JX 60, at 218:4-220:19.) In advocating for clinical trials of Viagra and other PDE5 inhibitors
 28 in cancer patients, Dr. Piazza did not suggest any issue or concern with a possible effect on

1 melanoma. (Piazza, DX 61.) In August 2018, Dr. Piazza was awarded a patent (U.S. Patent No.
2 10,039,764 B2, DX 62) “for a compound that’s a PDE10 inhibitor that could be co-administered
3 with sildenafil or tadalafil to treat melanoma in humans.” (Piazza Tr., JX 61, at 338:25-342:14.)

4 **E. Dr. Anand Ganesan**

5 **1. Background and Opinions Offered**

6 Dr. Anand Ganesan is an Associate Professor of Dermatology and Biological Chemistry at
7 the University of California at Irvine. He opines about Cialis only and cites only the Arozarena
8 and Dhayade studies in support of his primary opinion that “[t]he published literature provides
9 solid evidence that there is a causal link between sporadic use of PDE5 inhibitors and melanoma
10 growth and invasiveness.” (Ganesan Rep., JX 17, at 2, 5, 21.) His report does not analyze the
11 observational studies.

12 Dr. Ganesan’s opinions have morphed over time. In his report, he opines that PDE5
13 inhibitors can enhance both melanoma tumor invasion and tumor growth or proliferation. (*Id.* at
14 21.) At his deposition, however, Dr. Ganesan renounced any opinion concerning growth or
15 proliferation, testifying, “I accept that there’s no increase in proliferation” (Ganesan Tr., JX
16 56, at 29:22-31:16.) He repeated this position throughout the deposition. (*See, e.g., id.* at 31:17-
17 19, 51:19-23, 78:15-79:6.) Remarkably, Dr. Ganesan then retracted his retraction, submitting a
18 “deposition errata” that systematically sought to change his sworn deposition answers back to
19 what he included in his report (presumably with the assistance of Plaintiffs’ counsel). (Ganesan
20 Errata, JX 57.) For example, in his deposition errata, Dr. Ganesan attempted to edit his testimony
21 at 51:12-23 as follows (with his original responses in strike-through text and his replacement
22 responses in bold):

23 Q: Okay. And you’re not offering the opinion that PDE5 inhibitors cause
24 melanoma to form; correct?

25 A: No, I’m not offering that opinion. The opinion I’m offering is, is that PDE5
26 inhibitors accelerate the growth of melanomas – or cells that have the
27 mutation – melanocytes that have the mutations to generate melanoma
28 tumors.

Q: And when you use the term “growth,” you mean invasion.

1 A: ~~Invasion-Invasion.~~ **No. My opinion, as stated in my report, is that**
 2 **PDE5 inhibitors accelerate the growth and invasion of melanoma.**

3 Q: Okay. Not proliferation or tumor size.

4 A: ~~No-Invasion.~~ **Not proliferation. Growth and invasion.**

5 (See *Id.* at 194; Ganesan Tr., JX 56, at 51:12-23.)

6 2. Dr. Ganesan's Flawed Methodology

7 Regardless of whether he intends to opine on melanoma growth, invasion, or both, Dr.
 8 Ganesan's opinions in this case are inconsistent with his real-world conduct as a clinician and
 9 researcher. In the litigation setting, Dr. Ganesan claims that "taking a *single dose* [of PDE5
 10 inhibitor] would have an effect on increasing the invasive capacity of the cell." (Ganesan Tr., JX
 11 56, at 74:21-75:3 [emphasis added].) Outside of litigation, Dr. Ganesan never has shared this
 12 opinion with his medical students, colleagues, or any of the professional organizations of which he
 13 is a member. (*Id.* at 82:25-83:5, 117:23-118:3.) Equally notable is the gap between Dr. Ganesan's
 14 testimony in this case and his real-world approach to patient care: he never has told a patient that
 15 a single dose of PDE5 inhibitor can worsen melanoma. (*Id.* at 66:10-24.) He does not routinely
 16 review his patients' medication lists to see if they report using PDE5 inhibitors. (*Id.* at 64:15-
 17 65:10.) And he has told only a single patient that PDE5 inhibitors may cause melanoma to
 18 become more invasive – doing so after being retained in this litigation and immediately before
 19 proceeding to prescribe Viagra to the patient. (*Id.* at 62:13-63:2.)

20 Pressed to explain what science supports his claims in this litigation, Dr. Ganesan
 21 conceded the complete absence of any supportive human data. (*Id.* at 119:2-10.) As Dr. Ganesan
 22 explained, observational data will not suffice, because "[y]ou can't measure increased invasion in
 23 an epidemiology study." (*Id.* at 171:11-14.) He has not reviewed studies examining the effect of
 24 directly increasing the concentration of cGMP in melanoma cells (*id.* at 163:2-20), despite the fact
 25 that he opines that increased cGMP is how PDE5 inhibitors increase melanoma invasion. (*Id.* at
 26 23:6-24:16.) Instead, Dr. Ganesan's opinions rest solely on the Arozarena and Dhayade studies.

27 Dr. Ganesan acknowledges that the Arozarena study alone is insufficient to demonstrate
 28 biological plausibility because the only evidence of increased invasion was in a single *in vitro* cell

line. (*Id.* at 119:11-23, 166:3-167:13.) In short, the Arozarena study “needed to be corroborated by other literature” in the form of “additional . . . *in vitro* and *in vivo* studies” as well as “additional human studies to see if it was relevant.” (*Id.* at 115:12-18, 117:11-22.) Although Dr. Ganesan cites the Dhayade study for that supposed corroboration, he concedes that the Dhayade study never measured invasion. (*Id.* at 75:8-12, 137:6-22.) Moreover, Dr. Ganesan acknowledges numerous methodological limitations of the Dhayade study, including that: (1) the researchers added CNP to melanoma cells before ever adding Viagra; (2) they did not test PDE5 inhibitors alone without CNP in melanoma cells; and (3) human melanoma cells have no known source of CNP. (*Id.* at 37:3-38:5, 75:13-16, 161:10-15.)

Dr. Ganesan also concedes that it is impossible to demonstrate that any particular patient’s melanoma would be affected by a PDE5 inhibitor. (*Id.* at 74:15-20.) He cannot predict what percentage – if any – of PDE5 inhibitor users with melanoma will experience increased invasion. (*Id.* at 71:20-72:2, 75:17-76:14, 77:16-23.)

F. Dr. Rizwan Haq

1. Background

Dr. Rizwan Haq is a medical oncologist and researcher at Dana-Farber Cancer Institute. (Haq Rep., JX 9, at 8.) He opines about Viagra only. Dr. Haq spends most of his time on laboratory research investigating resistance to melanoma treatments. (Haq CV, JX 10, at 11; Haq Tr., JX 58, at 12:24-13:10.) He has a limited clinical practice, in which he spends half a day per week treating patients with late-stage, metastatic melanoma. (Haq CV, JX 10, at 11; Haq Tr., JX 58, at 93:17-94:20.)

2. Opinions Offered

Dr. Haq does not offer a causation opinion; he instead limits his opinion to biological plausibility. (Haq Tr., JX 58, at 48:7-15 [“A. My task was to evaluate the biological plausibility and not the causation. . . . Q. So you did not evaluate causation? A. Correct.”]; *see id.* at 48:16-49:12; 99:20-100:6; 241:8-242:2.) Outside of litigation, Dr. Haq reads observational studies and he relies on them in making clinical decisions for his patients. (*Id.* at 242:23-243:8). Yet, at his deposition, Dr. Haq would not discuss his views of the observational studies at issue, except to say

1 that he would make his patients “aware of the potential risk of using PDE5 inhibitors.” (*Id.* at
 2 246:20-247:20.) He would not quantify the magnitude of that risk or say whether he would advise
 3 his patients to stop taking PDE5 inhibitors. (*Id.* at 103:19-104:11; 246:20-247:20.) Dr. Haq
 4 recalls treating one patient who took a PDE5 inhibitor, but could not recall when that was or what,
 5 if anything, he told that patient about the alleged risks of PDE5 inhibitor use. (*Id.* at 98:5-11.)

6 Dr. Haq opines there is a biologically plausible mechanism by which Viagra can cause
 7 melanoma to progress. (*Id.* at 99:20-100:6.) When Dr. Haq refers to “melanoma progression,” he
 8 means an increase in melanoma cell growth and/or invasion. (*Id.* at 77:7-78:16.) He believes it is
 9 “biologically plausible that a single dose [of Viagra] can cause melanoma progression.” (*Id.* at
 10 175:13-18.) Even if a patient took only half of a Viagra pill ten years before being diagnosed with
 11 melanoma, in Dr. Haq’s view, it is biologically plausible that the half pill played a substantial role
 12 in the development of that individual’s melanoma, so long as the half pill was effective, meaning
 13 that it caused an erection. (*Id.* at 271:6-272:1.)

14 3. Dr. Haq’s Flawed Methodology

15 Dr. Haq has neither attempted to publish his opinion nor shared it with his colleagues at
 16 Dana-Farber. (*Id.* at 245:10-246:19; 250:7-17.) Dr. Haq did not consider the views of any major
 17 cancer organizations, cancer institutes, or regulatory agencies. (*Id.* at 87:24-88:9; 89:15-90:6;
 18 92:20-93:15.) Instead, he primarily relies on the Arozarena and Dhayade studies to support his
 19 biological plausibility opinion. (*Id.* at 172:6-19.)

20 Dr. Haq agrees that in the Arozarena study, only a single *in vitro* experiment involving a
 21 single human melanoma cell line, out of the ten cell lines studied, suggested that PDE5 inhibitors
 22 can increase melanoma cell invasion. (*Id.* at 128:1-16; 138:8-22; 147:13-21.) He also agrees that
 23 this finding was not observed in other cell lines. (*Id.* at 128:23-129:18.) Nonetheless, he purports
 24 to rely on all of the experiments in the Arozarena study – even the experiments that did not test
 25 PDE5 inhibitors – to conclude that it is biologically plausible that Viagra can increase melanoma
 26 cell invasion. (*Id.* at 124:1-14.) Dr. Haq concedes that his interpretation of the Arozarena study is
 27 at odds with the study’s authors, including the senior author and Pfizer’s expert, Dr. Marais (*id.* at
 28

1 179:6-22), whom he describes as “a world-leading expert in melanoma research” who leads “a
2 well-respected research group.” (Haq Rep., JX 9, at 15.)

3 As to the Dhayade study, Dr. Haq concedes that the cell experiments on which he relies
4 tested Viagra in combination with another compound, CNP, and never tested Viagra alone. (Haq
5 Tr., JX 58, at 189:10-190:16.) And he agrees that “it is unknown what th[e] sources [of CNP] are”
6 in people. (*Id.* at 212:13-213:5.) Dr. Haq acknowledges that “dose is crucial in interpreting these
7 [preclinical] experiments.” (*Id.* at 199:10-23.) A dose that is too low “can lead to a false
8 conclusion that the drug has no effect” and a dose that is too high can “have off-target effects, and
9 those would also lead to the false conclusion that there is an effect.” (*Id.* at 199:25-200:8.) Yet
10 Dr. Haq did not evaluate the doses of Viagra used in the mouse experiments in the Dhayade study.
11 (*See* Haq Rep., JX 9, at 17-18, 21-22.) He testified that the 200 mg/kg dose was appropriate
12 simply because the researchers provided evidence that the dose resulted in an increase in cGMP
13 levels in the mice. (Haq Tr., JX 58, at 198:17-199:23.) By Dr. Haq’s logic, any dose at or above
14 the threshold dose required to increase cGMP levels was appropriate, and no dose could be too
15 high.

16 ARGUMENT

17 General causation examines “whether the substance at issue had the capacity to cause the
18 harm alleged.” *In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1133 (9th Cir. 2002).
19 Here, Plaintiffs have the burden to prove – with admissible expert testimony that satisfies *Daubert*
20 – that PDE5 inhibitors are capable of causing melanoma progression. *In re Bextra & Celebrex*
21 *Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1172 (N.D. Cal. 2007).

22 In *Daubert*, the Supreme Court tasked district courts with ensuring that expert testimony is
23 both reliable and relevant. 509 U.S. at 597. Pursuant to Federal Rule of Evidence 702, courts
24 must ensure that: (1) experts are qualified; (2) their “testimony is based on sufficient facts or
25 data”; (3) their “testimony is the product of reliable principles and methods”; and (4) they have
26 “reliably applied the principles and methods to the facts of the case.”

27 Reliability turns on whether the methodology underlying the testimony is scientifically
28 valid. *Daubert*, 509 U.S. at 600. In determining the reliability of expert testimony, courts may

consider: “(1) whether the scientific theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential error rate; and (4) whether the theory or technique is generally accepted in the relevant scientific community.” *Domingo ex rel. Domingo v. T.K.*, 289 F.3d 600, 605 (9th Cir. 2002) (citing *Daubert*, 509 U.S. at 593-94). Other relevant factors include whether the expert testimony is based on research conducted independent of litigation, *Daubert II*, 43 F.3d at 1317, whether the expert “meaningfully account[ed] for medical literature at odds with their testimony,” *McEwen v. Balt. Wash. Med. Ctr. Inc.*, 404 F. App’x 789, 791 (4th Cir. 2010), and whether the expert offers opinions that are contrary to the conclusions drawn by the scientists who actually performed the relevant research. *Joiner*, 522 U.S. at 146. Under *Joiner*, “a court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.” *Id.* For example, “[w]here an expert ignores evidence that is highly relevant to his conclusion, contrary to his own stated methodology, exclusion of the expert’s testimony is warranted.” *Mirena*, 2018 WL 5276431, at *22.

As set forth below, Plaintiffs’ experts’ opinions fail entirely to satisfy the standards set out in *Daubert* and its progeny. First, the opinions do not satisfy the *Daubert* hallmarks of reliable methods: they are not generally accepted, they go well beyond (or even outright contradict) the conclusions drawn by the authors of the studies on which the experts rely, and they have not been subjected to peer review. Second, Plaintiffs’ experts offer unreliable analyses of the clinical trial and observational study data. Finally, Plaintiffs’ experts’ biological plausibility opinions are based on cherry-picked findings from the available animal and petri dish experiments, which involved animal models that do not apply to humans, used massive doses of PDE5 inhibitors, and/or did not test PDE5 inhibitors alone. For these reasons, the Court should exclude Plaintiffs’ experts’ opinions in their entirety.

I. PLAINTIFFS' EXPERTS' OPINIONS SHOULD BE EXCLUDED BECAUSE THEY LACK KEY *DAUBERT* HALLMARKS OF RELIABILITY.

A. Plaintiffs' Experts' Opinions Are Not Generally Accepted.

“Widespread acceptance can be an important factor in ruling particular evidence admissible.” *Daubert*, 509 U.S. at 594. “[T]he Ninth Circuit routinely has considered the reliability of expert testimony against the backdrop of other scientists’ opinions.” *Carnegie Mellon*, 55 F. Supp. 2d at 1032 (citing *Daubert II*, 43 F.3d at 1319 (stating that experts must “show that they have followed the scientific method, as it is practiced by (at least) a recognized minority of scientists in their field”); *Lust*, 89 F.3d at 597 (finding testimony inadmissible because expert’s opinions were not accepted by others in his field)). An expert theory that “lacks any acceptance, let alone general acceptance, in the scientific community” is a clear indication of unreliable methods. *In re Mirena*, 2018 WL 5276431, at *9, 44 (excluding expert testimony accepted by “no medical organization or regulator or peer-reviewed scientific literature”).

Plaintiffs’ experts’ opinions lack any acceptance, let alone general acceptance, in the scientific community. None of the authors of the studies Plaintiffs’ experts cite have concluded that PDE5 inhibitors can cause melanoma progression. In fact, all of the studies expressly *disclaim* such a conclusion. Even the Li study, on which Plaintiffs’ experts rely heavily, emphasized that “[o]ur study cannot prove cause and effect” (Li, JX 90, at 969), and all of the authors of the subsequent observational studies agreed that their findings did not establish a causal relationship between PDE5 inhibitor use and melanoma; indeed, they suggested non-causal explanations for the small associations observed in some (but not all) of the studies. (*See supra* SOF § I.F.) The authors of the preclinical studies on which Plaintiffs’ experts rely similarly disclaim any proof of a causal relationship (Arozarena) or note the significant limitations of their work (Dhayade). (*See supra* SOF §§ I.D, I.G.)

The medical, scientific, and regulatory communities also do not accept that there is a causal relationship between PDE5 inhibitor use and melanoma. FDA and EMA examined the available data repeatedly and never recommended any warnings regarding melanoma or found that the safety profile of Viagra or Cialis had changed. (*See supra* SOF § I.H.) No medical

organization has concluded that PDE5 inhibitor use can cause melanoma progression. (*See supra* SOF § I.I.) In fact, as recently as April 2018, the American Academy of Dermatology informed its more than 20,000 members that “[r]esearch has not proven a causal relationship between the use of erectile dysfunction drugs and skin cancer risk.” (AAD, Practice Management Center, *Erectile dysfunction drugs and skin cancer*, Apr. 16, 2018, DX 49.) And, consistent with these views, researchers continue to study the use of PDE5 inhibitors for the *treatment* of various cancers, including melanoma. (*See supra* SOF §§ I.C, I.I.)¹⁶

Plaintiffs’ experts’ opinions “do not, to understate the point, reflect the consensus within the scientific community.” *Daubert II*, 43 F.3d at 1314. For this reason, the Court should be “wary” that Plaintiffs’ experts have not “faithfully applied” their methodologies, *In re Nexium*, 662 F. App’x at 530, and should exclude their opinions. *See Lust*, 89 F.3d at 598.

B. Plaintiffs’ Experts’ Opinions Rely On Interpretations Of Studies That Are At Odds With The Study Authors’ Own Interpretations.

Plaintiffs’ experts’ opinions also are directly contrary to the conclusions drawn by the scientists who conducted the research on which those opinions are based. It is unreliable for an expert to “analyze[] data that was not his own and reinterpret[] it in a manner inconsistent with the conclusions of those who originally generated it.” *Carnegie Mellon*, 55 F. Supp. 2d at 1040; *see Joiner*, 522 U.S. at 143-46.¹⁷ But that is exactly what Plaintiffs’ experts have done.

¹⁶ The widespread rejection of any causal link between PDE5 inhibitor use and melanoma progression highlights one of the critical distinctions between this case and the decision in *In re Roundup Products Liability Litigation*, in which the district court excluded some – but not all – of the plaintiffs’ experts. No. 16-md-02741, 2018 WL 3368534 (N.D. Cal. July 10, 2018). The *Roundup* decision emphasized that plaintiffs’ experts relied on assessments by IARC that the glyphosate in Roundup is “probably carcinogenic to humans” and is carcinogenic in laboratory animals. *Id.* at *1, *3, *16. The court deemed IARC’s conclusions regarding laboratory animals to be “quite relevant” and as evidence that plaintiffs’ assessments of the studies were “within the mainstream of scientific views. . . .” *Id.* at *16. Even with such evidence – starkly absent here – the court excluded three of the plaintiffs’ experts, and held it was a “close question” to not exclude the “shaky” causation opinions proffered by the plaintiffs’ three remaining experts. *Id.* at *36.

¹⁷ *See also McClain v. Metabolife Int’l, Inc.*, 401 F. 3d 1233, 1248 (11th Cir. 2005) (excluding expert who drew “unauthorized conclusions from limited data – conclusions the authors of the study do not make”); *In re Accutane*, 2009 WL 2496444, at *2 (“[W]hen an expert relies on the

1 The Supreme Court’s decision in *Joiner* is instructive. In *Joiner*, the plaintiff’s “theory of
 2 liability was that his exposure to [chemicals called] PCB’s and their derivatives ‘promoted’ his
 3 development of small-cell lung cancer.” 522 U.S. at 143. The district court “concluded that the
 4 four epidemiological studies on which [the plaintiff’s experts] relied were not a sufficient basis for
 5 [their] opinions” because the opinions were at odds with the analyses of the study authors
 6 themselves. *Id.* at 145. In one study, the study authors “were unwilling to say that PCB exposure
 7 had caused cancer among the workers they examined”; in another, “the authors . . . did not suggest
 8 a link between the increase in lung cancer deaths and the exposure to PCB’s”; and another found a
 9 “statistically significant increase in lung cancer deaths” among individuals exposed to PCBs, but
 10 the study authors attributed causation to another source. *Id.* at 145-46. The Supreme Court
 11 affirmed the district court’s decision excluding the plaintiff’s experts’ opinions as unreliable,
 12 explaining that “nothing in either *Daubert* or the Federal Rules of Evidence requires a district
 13 court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the
 14 expert.” *Id.* at 146. As one court put it, it is “axiomatic that causation testimony is inadmissible if
 15 an expert relies upon studies [or] publications, the authors of which were themselves unwilling to
 16 conclude that causation had been proven.” *Happel*, 602 F.3d at 826 (*quoting Huss*, 571 F.3d at
 17 459).

18 As in *Joiner*, Plaintiffs’ experts offer opinions that are directly at odds with those of the
 19 study authors. With respect to the human data, Plaintiffs’ epidemiology experts – Drs. Singh, Liu-
 20 Smith, and Ahmed – agree with the Li study authors that the study cannot prove cause and effect.
 21 (Singh Tr., JX 54, at 201:10-24; Liu-Smith Tr., JX 63, at 225:17-226:9; Ahmed Tr., JX 65, at
 22

23 studies of others, he must not exceed the limitations the authors themselves place on the study.”);
 24 *In re Mirena*, 2018 WL 5276431 at *22 (same); *Anderson v. Bristol Myers Squibb Co.*, No.
 25 CIV.A. H-95-0003, 1998 WL 35178199, at *11-12 (S.D. Tex. Apr. 20, 1998) (excluding expert
 26 who drew a “causation conclusion that the authors of the study never even reached in their
 27 published work”); *Jones v. U.S.*, 933 F. Supp. 894, 898 (N.D. Cal. 1996) (excluding experts who
 28 “claimed that their opinions were supported by numerous scientific articles, [however] a careful
 reading of these articles reveals that many of the authors came to different conclusions than
 Plaintiffs’ witnesses did”).

289:14-290:2.) They also concede that none of the authors of the other five observational studies or the six meta-analyses concluded that PDE5 inhibitors cause melanoma progression. (Singh Tr., JX 54, at 271:11-272:20, 297:14-298:1; Liu-Smith Tr., JX 63, at 88:9-15, 103:8-104:10, 317:16-318:14; Ahmed Tr., JX 65, at 289:14-290:2, 401:2-14; *see supra* SOF § I.F.) In fact, Dr. Liu-Smith admits that “[n]one of the epidemiology can prove cause and effect.” (Liu-Smith Tr., JX 63, at 226:1-9.) Yet Plaintiffs’ experts rely on those studies in support of their opinion that a causal relationship exists. In doing so, they resoundingly “exceed the limitations the authors themselves place” on their own studies. *In re Accutane*, 2009 WL 2496444, at *2. That inconsistency is a signal of unreliable methods. *See Joiner*, 522 U.S. at 146.

Plaintiffs’ biological plausibility opinions fare no better. Plaintiffs’ experts all rely on the Arozarena study as evidence of a biologically plausible mechanism by which PDE5 inhibitors can increase melanoma progression. In fact, in Plaintiffs’ experts’ reports – which the experts submitted before they knew Dr. Marais was serving as an expert for the defense – Plaintiffs’ experts describe Dr. Marais as “a world-leading expert in melanoma research” who leads a “well-respected research group.” (Haq Rep., JX 9, at 15; *see also* Ganesan Rep., JX 17, at 14 [describing Dr. Marais as “a highly respected expert in melanoma biology”]; Piazza Rep., JX 5, at 14 [describing the Arozarena study as “from a well-respected laboratory led by Richard Marais”]).

Yet Plaintiffs’ experts overlook or disagree with the conclusions of Dr. Marais and his colleagues, who wrote in their article that “we do not perceive [the use of PDE5 inhibitors] to be a problem” and who cautioned that their data “should be interpreted with care, and we do not immediately suggest that PDE5A inhibitors will drive melanoma metastasis.” (Arozarena, JX 85, at 55.) As Dr. Marais explains in his report, “when properly understood, my research does not support the Plaintiffs’ experts’ theories, and there is no reliable evidence that sildenafil or other PDE5 inhibitors can cause melanoma progression.” (Marais Rep., JX 27, at 1; *see also* Marais Tr., JX 71, at 117:23-119:4 [“We built a hypothesis, we tested that in vivo and we found that that hypothesis failed.”]; *id.* at 238:3-8 [noting that his lab had “shown that we couldn’t get metastasis in vivo in mice treated with sildenafil”]; *supra* SOF § I.D.) Plaintiffs’ experts acknowledge that their interpretations of the Arozarena study differ from those of Dr. Marais and his co-authors

(Haq Tr., JX 58, at 179:6-22; Piazza Tr., JX 60, at 139:7-146:11), but offer no real explanation other than that they “respectfully disagree” with the study authors. (Haq Tr., JX 58, at 179:16-22; *see also* Piazza Tr., JX 60, at 148:21-150:15.) Plaintiffs’ experts thus interpret the Arozarena study “in a manner inconsistent with the conclusions” of the study authors themselves. *Carnegie Mellon*, 55 F. Supp. 2d at 1040.

Plaintiffs’ experts similarly draw conclusions from the Dhayade study without regard to the limitations identified by the study authors. The Dhayade study authors noted that the pathway they studied in B16 mice melanoma cells “is probably not universally conserved in all human melanomas”; that it still “needs to be established in future studies” whether CNP is present in human melanoma cells; and that “it is not clear whether the sildenafil concentration used in our experiments is also reached in patients.” (Dhayade, JX 87, at 2604, 2607, Fig. S5; Feil, JX 104, at 1; *see supra* SOF § I.G.) Plaintiffs’ experts nonetheless conclude that the study proves it is biologically plausible that PDE5 inhibitors promote the growth of melanoma in humans. In other words, the only connection between the data presented in the Dhayade study and Plaintiffs’ experts’ opinions is their own *ipse dixit*. *Joiner*, 522 U.S. at 146.

C. Plaintiffs’ Experts’ Opinions Have Not Been Subject To Peer Review.

Given that Plaintiffs’ experts’ opinions are contrary to those held by the study authors and the rest of the medical, scientific, and regulatory communities, Plaintiffs’ experts at least could have subjected their conflicting opinions to review by their scientific peers. *See Daubert II*, 43 F.3d at 1318 (“Establishing that an expert’s proffered testimony grows out of pre-litigation research or that the expert’s research has been subjected to peer review are the two principal ways the proponent of expert testimony can show that the evidence satisfies the first prong of Rule 702.”); *Daubert*, 509 U.S. at 593 (peer review “increase[s] the likelihood that substantive flaws in methodology will be detected”). But they did not seek to publish their opinions or otherwise subject them to peer review. (Singh Tr., JX 54, at 28:14-29:11; Liu-Smith Tr., JX 63, at 105:9-17; Ahmed Tr., JX 65, at 60:22-61:19; Haq Tr., JX 58, at 250:7-17.)

Even more troubling is the fact that none of Plaintiffs’ experts could recall even sharing with their colleagues their view that PDE5 inhibitors cause melanoma progression. (Ahmed Tr.,

JX 65, at 68:18-69:14; Ganesan Tr., JX 56, at 117:23-118:6; Liu-Smith Tr., JX 63, at 23:6-24:5; Piazza Tr., JX 60, at 41:16-20; Singh Tr., JX 54, at 28:14-30:23; *see also* Haq Tr., JX 58, at 98:13-99:7, 250:7-17.) In fact, when the opportunity arose, Dr. Liu-Smith chose to remain silent rather than subjecting her opinions to the scrutiny of her peers. (Liu-Smith Tr., JX 63, at 82:15-84:1.) Dr. Ganesan also chose not to participate in a discussion of the literature with his peers. (Ganesan Tr., JX 56, at 66:25-68:9.) Dr. Piazza is perhaps most egregious in this respect, as outside of this litigation he has published numerous peer-reviewed articles finding that PDE5 inhibitors can be used to *treat* various cancers, including melanoma, and has sought and obtained patents on such treatments. (*See supra* SOF §§ I.C, II.D.3.)

That Plaintiffs' experts' opinions have not been subject to peer review and publication is another indication that their opinions do not "meet[] at least the minimal criteria of good science." *Daubert II*, 43 F.3d at 1318. "[T]he absence of peer-reviewed publication is another factor in favor of excluding [Plaintiffs' experts'] testimony." *Carnegie Mellon*, 55 F. Supp. 2d at 1033-34.

II. PLAINTIFFS' EXPERTS' GENERAL CAUSATION OPINIONS ARE BASED ON UNRELIABLE ANALYSES OF HUMAN DATA AND SHOULD BE EXCLUDED.

Faced with the broad consensus in the medical, scientific, and regulatory communities that is contrary to their opinions, Plaintiffs' experts resort to unreliable analyses of the clinical trial data and published observational studies. In assessing a body of data, scientists employing a reliable methodology consider all of the available evidence. (*See* REF. MAN. at 554.) They then consider whether there is a valid association between exposure to a substance and a disease, or whether there are alternative explanations for any association that is observed, such as chance, bias, or confounding. (*See id.*) Because "*an association is not equivalent to causation*" (*id.* at 552 [emphasis in original]), scientists then analyze whether a valid association reflects a true causal relationship, which epidemiologists often assess through a framework called the Bradford Hill criteria. (*See id.* at 598-600; Liu-Smith Tr., JX 63, at 306:23-307:2; Restatement (Third) Torts § 28 cmt. (c)(3).) In each step of this process, Plaintiffs' experts fail to employ "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152.

Further, in conducting an analysis of the available data, scientists organize the evidence based on the strengths and limitations of each type of study. (*See* REF. MAN. at 723 [“A fundamental principle of evidence-based medicine” is that “the strength of medical evidence supporting a therapy or strategy is hierarchical.”].) “When ordered from strongest to weakest, systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic reviews of observational studies, single observational studies, physiological studies, and unsystematic clinical observations.” (REF. MAN. at 723-24.)

In their analysis of the human data, Plaintiffs’ experts ignore this hierarchy by unreliably analyzing – or overlooking entirely – data from Viagra and Cialis clinical trials. With regard to the lower-quality observational studies, Plaintiffs’ experts fail to reliably assess the totality of the evidence, do not reliably establish that there is a valid statistical association between the use of PDE5 inhibitors and melanoma, and do not reliably analyze whether the few statistical associations that were observed reflect a causal relationship.

A. Plaintiffs’ Experts Do Not Reliably Evaluate The Clinical Trial Data.

Plaintiffs’ experts either ignore data from the hundreds of clinical trials conducted by Pfizer and Lilly involving more than 60,000 men and women who took Viagra or Cialis (*see supra* SOF § I.B), or they analyze it in a way they admit is not scientifically valid. These experts’ failure to evaluate appropriately (or at all) the clinical trial data reflects the unreliability of their methods, especially in light of their “single pill” theory and their reliance on clinical trial data in other contexts. “Where an expert ignores evidence that is highly relevant to his conclusion, contrary to his own stated methodology, exclusion of the expert’s testimony is warranted.” *In re Mirena*, 2018 WL 5276431 at *22; *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) (same).

In a clinical trial, patients are assigned at random to receive either the study medication or a placebo (sugar pill), which minimizes the likelihood of baseline differences between the exposed and unexposed groups at the start of the study by distributing those differences evenly across both groups. (*See* REF. MAN. at 555; Ahmed Tr., JX 65, at 191:19-192:8.) At least some of Plaintiffs’ experts agree that randomized controlled trials are the “gold standard” for human research of

1 potential health effects of medications. (REF. MAN. at 555; *see* Liu-Smith Tr., JX 63, at 105:18-
2 24; Ahmed Viagra Rep., JX 13, at 13.)

3 Despite the advantages of randomized controlled clinical trials, two of Plaintiffs' three
4 epidemiology experts, Dr. Liu-Smith and Dr. Singh, made no effort to analyze the Viagra or Cialis
5 clinical trial data in reaching their opinions and did not even acknowledge the data in their reports.
6 This approach is at odds with the methodology used by FDA to evaluate any potential relationship
7 between PDE5 inhibitors and melanoma, which included careful review of the Viagra and Cialis
8 clinical trial data. (*See* Letter from Christine Nguyen, FDA Office of Drug Evaluation III, to
9 Pfizer Inc., June 3, 2016, DX 71, at 1-2; Lilly 2016 Safety Topic Report, DX 13, at 8.)

10 Plaintiffs' other epidemiology expert, Dr. Ahmed, conducted her own analysis of the
11 Viagra clinical trial data, but not the Cialis clinical trial data. (Ahmed Viagra Rep., JX 13, at 28;
12 Ahmed Cialis Rep., JX 14, *passim*.) Dr. Ahmed offered no explanation for why she analyzed one
13 set of clinical trial data but not the other. Regardless, at her deposition, Dr. Ahmed disclaimed her
14 analysis of the Viagra clinical trial data, explaining that she "didn't perform a full analysis"; her
15 cursory review did not meet the standard of a peer-reviewed publication; and she already had
16 reached her causation opinion before she analyzed the clinical trial data. (Ahmed Tr., JX 65, at
17 246:21-248:25; 250:25-251:9.) The reason is not difficult to discern: there was no difference in
18 the exposure-adjusted rate of melanoma events in patients who took Viagra compared to those
19 who took placebo. (*See supra* SOF § I.H; Witte Rep., JX 36, at 10-12.)

20 Plaintiffs' experts thus ignored or performed superficial reviews of the highest level
21 evidence (clinical trials), and instead put their emphasis on select lower quality evidence
22 (observational or preclinical studies). This is not a reliable methodology. *See In re Rezulin*, 309
23 F. Supp. 2d at 563; *In re Mirena*, 2018 WL 5276431, at *22 (same).

24 **B. Plaintiffs' Experts Do Not Reliably Evaluate The Observational Study Data.**

25 Plaintiffs' experts equally mishandle the observational studies. They cherry-pick within
26 the observational studies by relying heavily on the smallest, least reliable study with significant
27 limitations in its data source. They also do not adequately address the role of confounding by sun
28

1 exposure and detection bias. Finally, they do not apply the Bradford Hill criteria reliably to
 2 evaluate whether any association between PDE5 inhibitor use and melanoma is causal.

3 **1. Plaintiffs' Experts Do Not Reliably Assess The Totality Of The**
 4 **Observational Study Data.**

5 “Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship.”
 6 (REF. MAN. at 604; *see* Singh Tr., JX 54, at 201:10-24; Haq Tr., JX 58, at 250:24-251:21; Ahmed
 7 Viagra Rep., JX 13, at 14; Ahmed Tr., JX 65, at 261:22-262:13.) If a study finds a true effect of a
 8 medication, its results should be replicated consistently across multiple studies of similar design.
 9 (See REF. MAN. at 604; Haq Tr., JX 58, at 289:9-290:3; Singh Lipitor Tr., DX 56, at 351:3-22.)
 10 As a result, deference to a single study “is not a reliable way to reach a general causation opinion.”
 11 *In re Roundup*, 2018 WL 3368534, at *33. This tenet especially holds true where the study relied
 12 upon is an “epidemiological study which stopped well short of finding causation, recognizing that
 13 it had not controlled for major confounding variables[.]” *In re Mirena*, 2018 WL 5276431, at *31.
 14 In evaluating a body of evidence, therefore, an expert should assess the totality of available
 15 evidence – not just bits and pieces that support a particular conclusion – and evaluate how each
 16 study result fits within the complete body of scientific knowledge. (Haq Tr., JX 58, at 252:4-10;
 17 Singh Tr., JX 54, at 42:23-43:8.) A decision to “brush aside” contrary epidemiological findings
 18 departs from a reliable, rigorous methodology, *In re Mirena*, 2018 WL 5276431, at *32, and
 19 courts regularly exclude experts who do so.¹⁸ Even if an expert does mention all of the available
 20 observational data, merely summarizing the results of studies is not a methodologically reliable
 21 means to evaluate causation.¹⁹

22 _____
 23 ¹⁸ *See McEwen*, 404 F. App'x at 791-92 (upholding exclusion where experts “failed to
 24 meaningfully account for... literature at odds with their testimony”); *In re Bextra & Celebrex*, 524
 25 F. Supp. 2d at 1176 (“[R]ejecting or ignoring” unfavorable evidence “is not ‘good science.’”) (citation omitted); *MTX Commc'ns v. LDDS/WorldCom, Inc.*, 132 F. Supp. 2d 289, 293 (S.D.N.Y.
 26 2001) (excluding expert who omitted “major variables” from his analysis); *In re Rezulin*, 309 F.
 27 Supp. 2d at 563 (“[A]n expert may not pick and choose from the scientific landscape.”) (internal
 28 quotation marks omitted).

¹⁹ *See In re Nexium*, 662 F. App'x at 530 (upholding exclusion of testimony where the expert summarized the epidemiological literature, but did not explain how he “came to a different

1 In determining whether there is a statistical association between the use of PDE5 inhibitors
 2 and melanoma progression, Plaintiffs' experts who attempt to analyze the observational studies –
 3 Drs. Singh, Liu-Smith, and Ahmed – summarize the studies generally but place almost singular
 4 reliance on the Li study. They do so even though the Li study was the smallest study by far (*see*
 5 *supra* SOF §§ I.E, I.F), and even though they admit that the size of a study is an important factor
 6 in assessing the robustness of any statistical association. (*See* Singh Tr., JX 54, at 111:9-15;
 7 Ahmed Tr., JX 65, at 266:3-4.) Studies subsequent to Li, which were many times larger in terms
 8 of the people involved and the number of melanoma events, showed either much smaller
 9 associations or no statistical association at all. (*See supra* SOF § I.F; App. Table 3.) Plaintiffs'
 10 experts disregard the main findings – either no association, or a very weak association – in favor
 11 of cherry-picking one or two statistically significant sub-results, which is unreliable. *See In re*
 12 *Bextra & Celebrex*, 524 F. Supp. 2d at 1176 (excluding expert who reached a general causation
 13 opinion by “cherry-picking observational studies that support his conclusion and rejecting or
 14 ignoring the great weight of the evidence that contradicts his conclusion”). There are reasons why
 15 the study authors themselves refused to find that their results supported a causation conclusion;
 16 Plaintiffs' experts attempt to gloss over those reasons by selectively citing data.

17 Plaintiffs' experts also rely heavily on the risk estimate reported in the Li study (a relative
 18 risk of 1.84), even though the primary risk estimates are much lower in all the other observational
 19 studies (ranging from 1.01 to 1.21) and the meta-analyses (ranging from 1.12 to 1.13). (*See* App.
 20 Table 4.) In so doing, Plaintiffs' experts elevate the smallest observational study above the totality
 21 of available observational study data.

22 Plaintiffs' experts also “brush aside” secondary analyses contrary to a causal relationship
 23 reported in every one of the five subsequent, far larger studies than the Li study. (*See* Ahmed
 24 *Viagra Rep.*, JX 13, at 17-19 [in conducting causality analysis, considering only the Li study in

25 conclusion than the studies' authors,” or how the heterogeneity in risk estimates “affected his
 26 causal conclusion”); *In re Roundup*, 2018 WL 3368534, at *33 (excluding expert because
 27 “[a]lthough he summarized the relevant studies, he said little about how or whether they addressed
 28 possible bias or confounding, for instance”).

evaluating strength of association; citing no observational studies that examined specificity; citing only Li study for temporality; and citing no observational studies for dose-response analysis]; Singh Rep., JX 2, at 43-48 [in conducting causality analysis, citing only Li study for strength of association; failing to consider any observational studies when assessing specificity; and failing to cite any observational studies or PDE5 inhibitor data for dose-response analysis]; *see* App. Table 3 [showing the totality of the secondary analyses in the observational studies].) In fact, Drs. Singh and Ahmed both fail even to acknowledge in their reports that multiple observational studies contained results showing that men who took PDE5 inhibitors were *less* likely to have advanced melanomas than men who did not, a finding irreconcilable with their opinions. (*See* Loeb, JX 93, at 2452, Tbl. 2; Pottegard, JX 96, at 899, Tbl. 3.) This is not a reliable methodology. *In re Mirena*, 2018 WL 5276431, at *32. Thus, while Plaintiffs' experts pay lip service to the totality of the available observational studies, they do not reliably assess that totality in offering their causation opinions.

2. Plaintiffs' Experts Do Not Reliably Address Confounding And Bias.

Plaintiffs' experts fail to rule out the impact of confounding and bias in the associations that were observed. "[T]he Achilles' heel of observational studies is the possibility of differences in the two populations being studied with regard to risk factors other than exposure to the agent." (REF. MAN. at 556; *see* Singh Tr., JX 54, at 62:18-22, 68:20-25; Liu-Smith Tr., JX 63, at 328:9-23.) Observational studies typically are based on large databases, such as insurance company or prescription databases, which may have incomplete data, or from surveys, which are dependent on the recollection of the participants. (*See* Singh Tr., JX 54, at 109:6-16; 171:5-172:21, 174:1-175:4; Liu-Smith Tr., JX 63, at 200:11-23, 204:15-205:6.) As a result, even Plaintiffs' experts agree "there could be 1,001 reasons" for an observed, statistical association between the exposure and outcome in a given observational study, with a causal relationship being only one of those explanations. (Singh Tr., JX 54, at 67:2-68:4.) Accordingly, courts evaluating the admissibility of causation testimony based on observational studies have held that, to be reliable, an expert "must demonstrate that [he or she] has adequately accounted for obvious alternative explanations"

1 including confounding and bias. *In re Mirena*, 2018 WL 5276431, at *40 (quoting *U.S. Info. Sys.,*
 2 *Inc. v. Int’l Bhd. of Elec. Workers*, 313 F. Supp. 2d 213, 238 (S.D.N.Y. 2004)).²⁰

3 Plaintiffs’ experts do not heed that caution and do not reliably consider the impact of
 4 confounding and bias. The peer-reviewed literature and FDA and EMA concluded that the two
 5 obvious non-causal explanations for the observed associations between PDE5 inhibitor use and
 6 melanoma are: (1) confounding by UV exposure, as reflected in statistical but non-causal
 7 associations between PDE5 inhibitor use and outcomes that are caused by UV exposure (basal cell
 8 carcinoma, squamous cell carcinoma, and solar keratosis); and (2) detection bias due to
 9 differential rates of health screening and health seeking behaviors in men who took PDE5
 10 inhibitors compared to men who did not. (*See supra* SOF §§ I.F, I.H.) Plaintiffs’ experts fail to
 11 account for either of these non-causal explanations, and they ignore the conclusions of FDA and
 12 EMA that the presence of confounding and detection bias in these studies means that the studies
 13 do not provide support for their causation opinions.

14 For example, Dr. Ahmed ignores the results of the Matthews study related to solar
 15 keratosis, which suggested that future PDE5 inhibitor users are more likely to have significant sun
 16 exposure prior to ever taking a single pill. (*See generally* Ahmed Cialis Rep., JX 14; Ahmed
 17 Viagra Rep., JX 13 [containing no references to solar keratosis]; Ahmed Tr., JX 65, at 319:19-
 18 320:7, 320:17-321:4.) She similarly omits any reference to basal cell carcinoma or squamous cell
 19 carcinoma in her Cialis report and references each of these skin cancers associated with UV
 20 exposure only once in her Viagra report. (*See generally* Ahmed Cialis Rep., JX 14; Ahmed

21
 22 ²⁰ *See also U.S. v. Valencia*, 600 F.3d 389, 425 (5th Cir. 2010) (“Evidence of mere correlation,
 23 even a strong correlation, is often spurious and misleading when masqueraded as causal evidence,
 24 because it does not adequately account for other contributory variables.”); *In re Roundup*, 2018
 25 WL 3368534, at *8, *33 (noting that confounding must be considered in a reliable expert opinion
 26 assessing epidemiology evidence and excluding expert testimony where expert did not address
 27 how bias and confounding would impact his conclusion); *In re Prempro Prods. Liab. Litig.*, 738 F.
 28 Supp. 2d 887, 891 (E.D. Ark. 2010) (“observational studies are more susceptible to bias and other
 confounding factors, and so are less reliable than clinical studies”); *In re Lipitor*, 174 F. Supp. 3d
 at 916 (in assessing causation, an expert must ““first look for alternative explanations for the
 associations, such as bias or confounding factors””) (quoting REF. MAN. at 598-600).

1 Viagra Rep., JX 13; *see* Ahmed Tr., JX 65, at 318:8-20, 319:19-320:7 [stating “I don’t know that
 2 this is relevant” when asked about basal cell carcinoma and solar keratosis results]; *id.* at 188:13-
 3 15 [acknowledging she had not studied link between basal cell carcinoma and PDE5 inhibitors].)

4 Although Drs. Singh and Liu-Smith at least summarize this evidence in their reports, they
 5 do not factor these data into their analyses, and they say little about how or whether they addressed
 6 possible bias or confounding. Dr. Singh admitted at his deposition that he could not rule out the
 7 possibility that the Li study risk estimate was higher than all other studies due to confounding.
 8 (Singh Tr., JX 54, at 183:8-184:5.) He agreed that it could be “important to hypothesize whether
 9 there is an association between PDE5 inhibitors and basal cell carcinoma” in testing for the
 10 presence of confounding by sun exposure, but he admittedly failed to investigate this relationship
 11 further – despite data in almost every meta-analysis he considered showing that the relative risks
 12 observed for basal cell carcinoma and PDE5 inhibitor use *exceeded* the relative risk for melanoma
 13 and PDE5 inhibitor use. (*Id.* at 223:7-12; *see also id.* at 177:18-178:7, 266:1-20; Loeb JX 92, at
 14 Suppl. Fig. 2; Wang, JX 99, at 46464, Fig. 3; Tang, JX 98, at 486, Fig. 2; Deng, JX 86, at 219.
 15 Fig. 4; Feng, JX 88, at 4, Fig. 3.) To explain his failure to address these associations with non-
 16 melanoma skin cancers, Dr. Singh suggests that basal cell carcinoma and squamous cell carcinoma
 17 are associated with “a different kind of sun exposure. Cumulative sun exposure.” (Singh Tr., JX
 18 54, at 89:11-16). That assertion is not supported by any literature, and it contradicts the views of
 19 Plaintiffs’ melanoma experts. *See supra* note 13.

20 Dr. Liu-Smith follows a results-oriented approach to the negative control data, using it
 21 when it helped her argument, but dismissing it when it did not. Although she initially identified
 22 the Li study’s use of basal cell carcinoma as a negative control as a strength of the study
 23 (presumably because in the Li study there was no association seen with that negative control), she
 24 subsequently changed her position when evaluating the Loeb, Mathews, and Shkolyar studies. In
 25 those studies, where the negative control data did not support her opinion, Dr. Liu-Smith did an
 26 about-face and speculated that “PDE5 inhibitors might actually also be related to the development
 27 of basal cell carcinoma.” (Liu-Smith Tr., JX 63, at 114:2-20, 121:22-122:22.) Dr. Liu-Smith
 28 admits that no other scientist, including Plaintiffs’ other experts, agreed with this hypothesis. (*See*

1 *id.* at 123:9-14.) A causation opinion that is based on observational studies and that does not fully
 2 explore bias and confounding is “methodologically deficient” and should be excluded. *In re*
 3 *Mirena*, 2018 WL 5276431, at *40. Plaintiffs’ experts’ failure to reliably assess the basal cell
 4 carcinoma results is particularly striking, given that the associations reported in the meta-analyses
 5 were higher than those for melanoma, even though no expert believes PDE5 inhibitors cause basal
 6 cell carcinoma. (*See App. Table 4.*)

7 Plaintiffs’ experts also ignore evidence of detection and screening bias in reaching their
 8 causation opinions. *See Valentine v. Pioneer Chlor Alkali Co.*, 921 F. Supp. 666, 678 (D. Nev.
 9 1996) (excluding testimony as not “derived from acceptable scientific methodology” where expert
 10 made no attempt to isolate the effect of bias, examine impact of bias in observational studies, or
 11 account for the impact of such factors on the expert’s causation opinion). As discussed (*see supra*
 12 SOF § I.F), men who see their doctors more frequently may be screened for and diagnosed more
 13 frequently with melanoma, for reasons wholly unrelated to their use of PDE5 inhibitors. None of
 14 Plaintiffs’ experts analyze the implications of the Li study’s inability to adjust for the number of
 15 physical examinations of a patient to examine the extent of possible detection bias. (Li, JX 90, at
 16 968.) Dr. Singh “possibly” agreed with the Li study authors that possible differences in health
 17 status and lifestyle practices between Viagra users and non-users may have confounded their
 18 findings. (Singh Tr., JX 54, at 181:12-24.) At the same time, though, he discounted studies that
 19 found PDE5 inhibitor use was associated with decreased colorectal cancer and other indicia of
 20 increased health care access and health-seeking behavior that could bias the results against patients
 21 taking PDE5 inhibitors. (Singh Tr., JX 54, at 181:12-24, 217:21-218:21, 238:4-240:14.) Nor do
 22 Plaintiffs’ experts address the implications of the Pottegard study, which found that men who took
 23 PDE5 inhibitors had more interactions with the healthcare system, likely resulting in earlier
 24 melanoma detection. (*See e.g.*, Pottegard, JX 96, at 898-99; Singh Tr., JX 54, at 217:21-218:21;
 25 Liu-Smith Rep., JX 20, at 23-24; Ahmed Cialis Rep., JX 14 [referring to Pottegard study only
 26 once in text of her report].)

27 Thus, although Plaintiffs’ experts agree with “widely accepted principles of medical
 28 research” regarding the limitations of observational studies, their conclusions are “unfaithful to

these precepts.” *In re Mirena*, 2018 WL 5276431, at *31. Because Plaintiffs’ experts have “said little about how or whether they addressed possible bias or confounding,” especially in the observational studies that came after the Li study, the Court should exclude their testimony. *In re Roundup*, 2018 WL 3368534, at *33; *see also In re Mirena*, 2018 WL 5276431, at *40 (for testimony to be reliable, an expert ““must demonstrate that [he or she] has adequately accounted for obvious alternative explanations”” including confounding and bias) (quoting *U.S. Info. Sys.*, 313 F. Supp. 2d at 238); *see also In re Lipitor*, 174 F. Supp. 3d at 916 (in assessing causation, an expert must ““first look for alternative explanations for the associations, such as bias or confounding factors””) (quoting REF. MAN. at 598-600); *U.S. v. Valencia*, 600 F.3d 389, 425 (5th Cir. 2010) (“Evidence of mere correlation, even a strong correlation, is often spurious and misleading when masqueraded as causal evidence, because it does not adequately account for other contributory variables.”).

3. Plaintiffs’ Experts Do Not Reliably Use The Bradford Hill Criteria To Evaluate Whether Any Association Between The Use Of PDE5 Inhibitors And Melanoma Is Causal.

It is only after scientists have established a valid association and have ruled out alternative explanations for the association (such as chance, bias, and confounding) that they assess whether the association reflects a true cause-effect relationship, occasionally using the Bradford Hill criteria.²¹ “There is no formula or algorithm that can be used to assess whether a causal inference is appropriate” based on the criteria, and “the existence of some factors does not ensure that a causal relationship exists.” (REF. MAN. at 600; *see also Singh Rep.*, JX 2, at 43 [noting that the

²¹ The Bradford Hill criteria are: (1) strength of association; (2) consistency; (3) specificity; (4) temporality; (5) biological gradient or dose-response; (6) biological plausibility; (7) coherence with other scientific knowledge; (8) experimental evidence; and (9) analogy. (Bradford Hill, PROCEEDINGS OF THE ROYAL SOCIETY MED. 1965;58:295, JX 102.) The REFERENCE MANUAL simplifies the Hill criteria and reorders them according to relative import, asking: (1) “Is there a temporal relationship?”; (2) “How strong is the association between the exposure and disease?”; (3) “Is there a dose-response relationship?”; (4) “Have the results been replicated?”; (5) “Is the association Biologically Plausible?”; (6) “Have alternative explanations been considered?”; (6) “What is the effect of ceasing exposure?”; (7) “Does the association exhibit specificity?”; and (8) “Are the findings consistent with other relevant knowledge?” REF. MAN. at 599-606.

Bradford Hill criteria are informative but not conclusive].) An expert must “reliably apply” the criteria, *In re Lipitor*, 174 F. Supp. 3d at 926, and because they are open-ended and an expert’s application of them potentially subjective, “each application is distinct and should be analyzed for reliability.” *In re Zolof*, 858 F.3d at 795. It is “all too easy for an expert to manipulate the Bradford Hill factors to support a desired conclusion of causation, and far too hard for an ensuing expert to replicate and rigorously test the expert’s analytic approach.” *In re Mirena*, 2018 WL 5276431, at *44. “To ensure that the Bradford Hill/weight of the evidence criteria is truly a methodology, rather than a mere conclusion-oriented selection process . . . there must be a scientific method of weighting that is used and explained” as to the relative contributions of each of the criteria. *In re Zolof*, 858 F.3d at 796 (internal quotation marks omitted); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 607 (D.N.J. 2002) (same), *aff’d*, 68 F. App’x 356 (3d Cir. 2003).

None of Plaintiffs’ three experts who invoke the Bradford Hill criteria – Drs. Singh, Liu-Smith, and Ahmed – provide a method for ranking the relative significance of individual criteria. (See Singh Tr., JX 54, at 280:3-281:11; Liu-Smith Tr. at 305:10-17; Liu-Smith Rep. at 34-35; Ahmed Tr., JX 65, at 353:10-354:8.) Instead, all three generally pronounce each criterion as satisfied or unnecessary to demonstrate causation in this instance. (See, e.g., Singh Rep., JX 2, at 43-48; Liu-Smith Rep., JX 20, at 34-35; Ahmed Cialis Rep., JX 14, at 12-13; Ahmed Viagra Rep., JX 13, at 17-18.) “Such a ‘check-the-box approach’ to the application of a nine-factor test . . . obscures the expert’s weighting of the various factors.” *In re Mirena*, 2018 WL 5276431, at *44. An analysis that does not prioritize among the various factors “almost entirely prevents the finder of fact, or other experts seeking to validate or check [the expert’s] work, from conducting a meaningful and informed review.” *Id.* at *28; *see also id.* at *26, *44. In particular, contrary to generally accepted principles and even Dr. Singh’s own prior testimony (*see supra* SOF § II.A.3), Plaintiffs’ experts unreliably downplay the importance of the lack of strength of the associations reported in the observational studies, the lack of a dose-response relationship, and the lack of specificity. (The criterion of biological plausibility is discussed separately in Section III, below.)

Plaintiffs’ Experts Do Not Reliably Assess The Weak Associations Observed In Some (But Not All) Studies. It is generally accepted in epidemiology that “[t]he higher the relative risk, the greater the likelihood that the relationship is causal.” (REF. MAN. at 602.) In the context of an observational study, a relative risk or odds ratio less than 2.0 is considered a “weak association.” (Singh Tr., JX 54, at 106:12-16; *see* REF. MAN. at 612, 612 n.193 [describing 2.0 rule and its proposed use for general causation given “the likelihood that an association less than 2.0 is noise rather than reflecting a true causal relationship”] [citations omitted]; *see also* Singh Initial Lipitor Rep., DX 53, at 34; Liu-Smith Tr., JX 63, at 137:21-138:2 [stating that lower relative risks require cautious interpretation]; Singh Lipitor Tr., DX 56, at 226:11-18 [stating that all studies become less reliable as to causation as you get closer to a relative risk of 1.0].) Although lower relative risks can reflect causality in some instances, “the epidemiologist will scrutinize such associations more closely because there is a greater chance that they are the result of uncontrolled confounding or biases.” (REF. MAN. at 602.)

Drs. Singh, Liu-Smith, and Ahmed all downplay the importance of the strength of association factor and suggest that a causal relationship can exist even if the reported associations are weak. (*See* Singh Rep., JX 2, at 43-44; Liu-Smith Rep., JX 20, at 34-35; Ahmed Cialis Rep., JX 14, at 12-13; Ahmed Viagra Rep., JX 13, at 17-18.) This is obviously a results-oriented approach, as *none* of the observational studies’ primary results reported a risk ratio above 2.0; many of the primary results were not even statistically significant; and all of the meta-analyses of the studies yielded risk ratios of barely above 1.0. (*See supra* SOF § I.F; App. Tables 3 & 4.) Given these very low risk ratios, it would be “a stretch to conclude” that the association between the use of PDE5 inhibitors and melanoma is “strong.” *In re Roundup*, 2018 WL 3368534, at *21.

To get around that inherent limitation in the data, Drs. Singh and Ahmed cherry-pick sub-analyses and/or the highest reported relative risks to achieve their desired result. For example, Dr. Singh cites only the Li study risk estimate of 1.84, which, not coincidentally, is the highest primary risk estimate of any study. (Singh Rep., JX 2, at 44.) Even that relative risk – which is less than 2.0 – is one he admits is “weak.” (Singh Tr., JX 54, at 106:12-16.) The Li study also has the smallest number of melanoma cases and widest confidence intervals (reflecting the greatest

1 uncertainty in their results) of all the observational studies. (*See id.* at 186:20-187:1; 187:10-21.)
 2 Similarly, when discussing the “strength of the association” for Viagra, Dr. Ahmed cites, without
 3 justification, only risk estimates from two subgroup analyses in the Li study, dismissing the much
 4 lower risk estimates in the remaining literature with the conclusory comment that “[s]everal
 5 authors observed more modest [odds ratios] in examining associations between sildenafil and
 6 melanoma than Li et al.” (Ahmed Viagra Rep., JX 13, at 17-18.)

7 It is not a reliable scientific method to prefer one study over many that have contradictory
 8 results simply because that study purports to support the expert’s conclusion. *See In re Bextra &*
 9 *Celebrex*, 524 F. Supp. 2d at 1177 (excluding testimony where expert attempted to justify “heavy
 10 reliance” on a single study “by asserting that it is the ‘best designed’ of all the observational
 11 studies” based on the cohort on which it was based and the fact it was a prospective study); *In re*
 12 *Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 891-92 (E.D. Ark. 2010) (excluding testimony
 13 where, “when reviewing these studies, [the expert] focused on those subgroups with the greatest
 14 risk, while discounting subgroups where [the medication] had no statistically significant effect”
 15 and noting that “selective presentation” of results to suggest strength of association “raises
 16 substantial doubt” about whether the expert “used reliable methods when evaluating scientific
 17 literature”).

18 Dr. Liu-Smith, by contrast, lists for consideration each sub-analysis involving Cialis in her
 19 “strength of association” discussion, but inaccurately characterizes that evidence. She notes that
 20 “there are several statistically significant increases reflected in the data” and at the same time
 21 ignores that there are three times as many non-significant results. (Liu-Smith Rep., JX 20, at 34-
 22 36.) Dr. Liu-Smith’s willingness to consider *any* result over 1.0 as indicative of strength of
 23 association correlates with her reluctance to acknowledge the basic principle that larger relative
 24 risk ratios are more likely to be causal. (*See* Liu-Smith Tr., JX 65, at 43:2-46:22; 134:24-135:20;
 25 307:11-309:21.) This departure from normal epidemiological practice and unwillingness to
 26 consider contrary data indicates an unreliable, results-driven methodology.

27 ***Plaintiffs’ Experts Do Not Reliably Assess The Lack Of A Dose-Response Relationship.***

28 A dose-response relationship means that the greater the exposure, the greater (or lower, if

1 protective) the risk of disease. (REF. MAN. at 603.) If an association is truly causal, then “[a]
2 greater amount of exposure should typically lead to a greater incidence of the outcomes.” (Singh
3 Rep., JX 2, at 46.) Cumulative exposure to a medication – the total dose a patient takes over time
4 – is “the single most important factor to consider in evaluating whether an alleged exposure
5 caused a specific adverse effect.” David Eaton, *Scientific Judgment and Toxic Torts*, 12 J.L. &
6 POL’Y 5 at 11.

7 Of the five observational studies of PDE5 inhibitors that analyzed dose-response data,
8 none found a consistent trend. (See Witte Rep., JX 36, at 26-28; App. Table 3.) For example, the
9 Loeb study found its only statistically significant relative risk at the *lowest* degree of exposure (a
10 single prescription), while the Matthews study found that the highest exposure had the *lowest*
11 relative risk – both precisely opposite what would be expected in a dose-response relationship.
12 (Loeb, JX 93, at 2451; Matthews, JX 94, at 6, 9.) The Lian study, which analyzed both number of
13 prescriptions and number of pills, found the lowest relative risk for each analysis to be the middle-
14 dose category. (Lian, JX 91, at 811.) The meta-analyses that evaluated dose also concluded there
15 was no evidence of a dose-response relationship. (Deng, JX 86, at 218; Han, JX 89, at 715-16;
16 Loeb, JX 92, at 2; Tang, JX 98, at 487; Witte Rep., JX 36, at 33-34.)

17 Plaintiffs’ experts differ wildly in their analyses of the dose-response data, but none were
18 willing to say that a dose-response relationship was reliably demonstrated. Dr. Singh concedes
19 that “we do not have evidence of a dose-response gradient” in the PDE5 inhibitor and melanoma
20 data. (Singh Rep., JX 2, at 46; *see also* Singh Tr., JX 54, at 268:8-269:16; 270:11-271:10; 287:13-
21 20.)

22 Dr. Ahmed states in her Viagra report that “dose-response was seen in some [Lian,
23 Pottgard] but not all of the reports.” (Ahmed Viagra Rep., JX 13, at 19.) At her deposition,
24 however, she admitted that none of the data she cites satisfies the standard required under basic
25 epidemiological methodology – and that she herself has used outside of litigation – to conclude
26 that a dose-response relationship exists. (See Ahmed Tr., JX 65, at 196:4-9; 302:20-24; 313:18-
27 314:23; 325:20-326:8.) The most she was willing to say in response to direct questioning as to
28 whether a dose-response relationship existed was that there were “examples of elevated dose

1 leading to risk, elevated risks” but “other examples where perhaps that’s not the case.” (*Id.* at
2 384:13-385:8.) Dr. Ahmed also was “not sure that [she], point blank, agree[s] with [Dr. Singh’s
3 testimony that there is no evidence of dose-response], but [she] referenced it because it’s not
4 contrary to [her] thought processes.” (*Id.* at 382:22-383:20.)

5 Dr. Liu-Smith, like Dr. Singh, admits there is no dose-response relationship between PDE5
6 inhibitors and the development of melanoma. (*See* Liu-Smith Tr., JX 63, at 189:7-190:4.) She
7 hypothesizes, however, without any evidence or support, that a non-linear, atypical dose response
8 relationship may be present in the data. (*See* Liu-Smith Rep., JX 20, at 38.) Dr. Liu-Smith was
9 not able to put forward any evidence in favor of any particular relationship, but she asserts
10 nonetheless that “clearly there is something going on.” (Liu-Smith Tr., JX 63, at 189:21-190:4.)
11 Her wholly speculative claim is inconsistent with the conclusions of Plaintiffs’ other experts and
12 with the available data.

13 Plaintiffs’ experts’ “single pill” theory is emblematic of the unreliability of their analysis
14 and a flawed attempt to address the lack of a dose-response relationship. Because the human data
15 do not demonstrate an increased risk of melanoma with increased exposure (a hallmark of
16 causation), Plaintiffs’ experts claim that taking a single pill can cause the purported effect. They
17 do not cite any evidence showing even a statistical association between the ingestion of a single
18 PDE5 inhibitor pill and melanoma – nor could they, since that evidence does not exist. They
19 admit that the Li study did not include information on the amount of Viagra taken by the men in
20 the study (Singh Tr., JX 54, at 163:7-18), nor was the study designed to assess whether a man who
21 took a single pill of Viagra ten years earlier developed melanoma. (*Id.* at 163:19-164:7.) The
22 Lian and Pottegard studies did examine the relationship between melanoma and the number of
23 pills taken, but neither study examined use of a single pill. (*See* Lian, JX 91, at 811, Tbl. 2;
24 Pottegard, JX 96, at 898, Tbl. 2.) When asked what studies in humans support Plaintiffs’ experts’
25 single-pill theory, Dr. Piazza admitted, “I don’t think those studies have been done.” (Piazza Tr.,
26 JX 61, at 385:14-25.) The closest any observational study came to such an analysis was the Lian
27 study, which showed no statistical association between melanoma and men who took one to four
28 PDE5 inhibitor pills. (Lian, JX 91, at 811, Tbl. 2.) That Plaintiffs’ experts are willing to offer a

single-pill theory when the very studies they cite do not analyze single-pill exposure at all demonstrates the unreliability of the methods by which they reach their opinions.

Plaintiffs’ Experts Do Not Reliably Assess The Lack Of Specificity. Associations are more likely to be causal when they are specific. (*See* REF. MAN. at 605-06 (“The vast majority of agents do not cause a wide variety of effects.”).); *In re Actos (Pioglitazone) Prods. Liab. Litig.*, No. 12-cv-00064, 2013 WL 6825953, at *12 (W.D. La. Dec. 20, 2013) (courts adopt “strong skepticism” of causation absent specificity between an exposure and a single disease). In addition to demonstrating the presence of confounding by sun exposure, the associations observed between the use of PDE5 inhibitors and non-melanoma skin cancers such as basal cell carcinoma suggest that there is no specificity in the alleged relationship between PDE5 inhibitors and melanoma. Plaintiffs’ experts either admit there is no specificity (*see* Singh Tr., JX 54, at 123:14-20), fail to consider the statistical associations observed with non-melanoma skin cancers (*see* Ahmed Tr., JX 65, at 188:13-15, 373:9-13), or misunderstand the concept of specificity. (*See* Liu-Smith Rep., JX 20, at 36-37.) In each instance – as with strength of association and dose-response – Plaintiffs’ experts instead suggest that specificity is not important in finding a causal relationship (Singh Rep., JX 2, at 45; Singh Tr., JX 54 at 123:3-20; Ahmed Viagra Rep., JX 12, at 18; *see generally* Ahmed Cialis Rep. [nowhere discussing specificity]; Liu-Smith Rep., JX 20, at 27), again demonstrating their results-oriented methodologies.

In short, in claiming that the Bradford Hill criteria support their conclusions, Drs. Singh, Ahmed, and Liu-Smith have not reliably applied the criteria. They do not prioritize the criteria, suggest a criteria ranking that differs from Dr. Singh’s prior statements, or they ignore or downplay the most important criteria, such as strength of association and dose-response relationship, simply because those factors do not support their opinions here.

III. PLAINTIFFS’ EXPERTS’ BIOLOGICAL PLAUSIBILITY OPINIONS ARE BASED ON UNRELIABLE ANALYSES OF THE PRECLINICAL DATA AND SHOULD BE EXCLUDED.

If the Court agrees that, for the reasons discussed above, Plaintiffs’ experts’ causation opinions are inadmissible, it need not reach the admissibility of their biological plausibility opinions. That is because “biological plausibility, without more, cannot establish general

causation.” *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018) (citations omitted); *see also In re Roundup*, 2018 WL 3368534, at *17 (plaintiffs may not “rely[] on mechanistic studies alone to justify their experts’ causal inferences”). Nonetheless, these opinions – which are based on preclinical studies in animals and petri dishes and are at odds with the study authors’ own interpretations of the studies – are likewise not the product of a reliable methodology under *Daubert* and therefore should be excluded.²²

A. Plaintiffs’ Experts Cherry-Pick Within And Among The Available Studies.

An expert may not “pick and [choose] from the scientific landscape and present the Court with what he believes the final picture looks like.” *Lust*, 89 F.3d at 596; *see also In re Bextra & Celebrex*, 524 F. Supp. 2d at 1176 (excluding expert who reached a general causation opinion by “cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion”); *Carnegie Mellon*, 55 F. Supp. 2d at 1039 (excluding expert who “selectively chose his support”). As Plaintiffs’ experts agree, it is improper to draw a conclusion about biological plausibility based on a single study, or experiment, or *in vitro* experiments alone. (See Ganesan Tr., JX 56, at 116:17-117:22, 119:11-23; Haq Tr., JX 58, at 211:20-212:11, 250:24-251:21, 252:4-10.) Yet that is exactly what Plaintiffs’ experts have done, as they cherry-pick both within and among the preclinical studies.²³ In essence, Plaintiffs’ experts rely solely on a single experiment within the Arozarena study (with respect to invasion) and on the Dhayade study (with respect to growth), while ignoring the limitations noted by the authors themselves and decades of contradictory studies.

²² Dr. Haq offers an opinion only on biological plausibility, *not* causation. (Haq Tr., JX 58, at 48:7-49:12, 78:4-10.) Dr. Singh appears to disclaim expertise in biological plausibility. (See, e.g., Singh Tr., JX 54, at 149:16-150:11 [stating that an understanding of the pathway by which melanoma develops is “beyond my expertise”]; *id.* at 152:15-153:6 [testifying that whether Dhayade and Arozarena studies support theories of proliferation and/or metastasis “is really not my area of expertise”].)

²³ In contrast to Plaintiffs’ five other experts, Dr. Ahmed goes to the other extreme, boldly claiming that every single experiment in every animal and cell study supports her theory of biological plausibility. (Ahmed Tr., JX 65, at 140:22-141:2 [testifying that “all of the data that I looked at supports my theory, whether or not it has a positive result or a negative result”].)

1 In a remarkable example of cherry-picking within an individual study, Plaintiffs’ experts
 2 rely on a single experiment in the Arozarena study involving PDE5 inhibitors to support their
 3 invasion theory, while discounting multiple contrary findings from the same study. (Piazza Rep.,
 4 JX 5, at 15-16, 18; Ganesan Rep., JX 17, at 13; Haq Rep., JX 9, at 15; Piazza Tr., JX 60, at 97:6-
 5 98:4, 100:13-101:14, 117:20-118:20, 128:19-22; Ganesan Tr., JX 56, at 144:4-145:2, 146:6-21,
 6 166:21-167:2; Haq Tr., JX 58, at 147:13-21, 157:16-25, 159:6-16, 161:20-162:12; Ahmed Tr., JX
 7 65, at 150:12-21; *see supra* SOF § I.D.) Plaintiffs’ experts’ selective reliance on a single *in vitro*
 8 experiment – while ignoring or failing to explain why the result was not replicated in other
 9 melanoma cells or mice in the same study – is “hardly scientific.” *Lust*, 89 F.3d at 596. Indeed,
 10 that is exactly why Dr. Marais was “indignant” that Plaintiffs cited his work in support of their
 11 claims. (*See supra* SOF § I.D.)

12 Plaintiffs’ experts also cherry-pick among studies. With respect to growth, they ignore
 13 studies showing that PDE5 inhibitors significantly decrease or have no effect on the growth of
 14 melanoma cells. (*See supra* SOF § I.G & n.9.) They also dismiss a vast body of literature
 15 spanning two decades that tested PDE5 inhibitors in melanoma and other cancer cells and showed
 16 the medications have either an anti-cancer effect or no effect at all. (*See supra* SOF §§ I.C, I.I;
 17 II.D.3.) And no Plaintiffs’ expert considered Dr. Piazza’s two decades of patents and publications
 18 demonstrating anti-cancer effects of PDE5 inhibition in dozens of human cancer cell lines,
 19 including multiple melanoma cell lines. (*See supra* SOF §§ I.C; II.D.3.) Plaintiffs’ experts
 20 likewise ignore or dismiss data from recent clinical trials using PDE5 inhibitors for the treatment
 21 of melanoma and other cancers, which would have been unethical to conduct if the medical
 22 community believed these medications caused melanoma progression. (*See supra* SOF § I.I.)

23 At most, Plaintiffs’ experts offer cursory analyses of this contradictory literature, do not
 24 explain why they discount it, or admit that it is “not consistent” with their opinions. (*See* Piazza
 25 Tr., JX 61, at 367:13-16; *see also* Ganesan Rep., JX 17, at 19; Haq Rep., JX 9, at 19-20; Haq Tr.,
 26 JX 58, at 117:11-118:6, 114:15-116:14; Ahmed Tr., JX 65, at 158:5-19.) They also conclude –
 27 without further explanation – that the “clinical relevance” of this particular preclinical literature is
 28 “unclear” (Ganesan Rep., JX 17, at 19; Piazza Rep., JX 5, at 30), and yet they have no problem

1 finding clinical relevance in the preclinical experiments conducted in the Arozarena and Dhayade
 2 studies. Plaintiffs' experts' selective reliance on an isolated, non-replicated *in vitro* experiment in
 3 the Arozarena study and the Dhayade study is not a reliable, scientifically-based methodology.
 4 *Carnegie Mellon*, 55 F. Supp. 2d at 1039.

5 **B. Preclinical Studies Do Not Reliably Predict Effects in Humans.**

6 "Federal courts have consistently cautioned against extrapolation of human effects from
 7 animal [and cell] studies." *In re Prempro*, 738 F. Supp. 2d at 894 (citing *Joiner*, 522 U.S. at 144;
 8 *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1313-14 (11th Cir. 1999); *In re Paoli R.R. Yard*
 9 *PCB Litig.*, 35 F.3d 717, 743 (3d Cir. 1994)). Animal (*in vivo*) and cell (*in vitro*) studies have a
 10 number of critical limitations. Experts offering opinions based on preclinical studies must take
 11 these limitations into account and explain "how and why [they] could have extrapolated their
 12 opinions from . . . seemingly far-removed animal [and cell] studies." *Joiner*, 522 U.S. at 144.

13 *In vivo* studies require extrapolating from animals (which often are genetically modified) to
 14 humans, where differences in absorption, metabolism, and other unknown factors result in
 15 interspecies variation in responses. (REF. MAN. at 563.) It also is difficult to predict the effects of
 16 medications observed in animals at clinically relevant doses in humans, given that "the high doses
 17 customarily used in animal studies require consideration of the dose-response relationship and
 18 whether a threshold no-effect dose exists." (*Id.*; see Haq Tr., JX 58, at 176:24-177:11 [preclinical
 19 studies "should use doses that engage the pathway comparably to their use in people"]; *id.* at
 20 283:24-284:10 [dosing in animal studies is "absolutely critical in determining how to interpret an
 21 experiment" because "[t]oo high a dose can lead to off-target effects" while "[t]oo low a dose can
 22 falsely lead to the conclusion that the drugs have no effect"].) For these reasons, animal data
 23 alone are insufficient to establish causation (see Ahmed Tr., JX 65, at 182:9-25), and
 24 "extrapolation from animal studies to humans cannot be done uncritically." *In re Rezulin Prods.*
 25 *Liab. Litig.*, 369 F. Supp. 2d 398, 407 (S.D.N.Y. 2005).

26 Extrapolating from *in vitro* studies is even more difficult. Cells used in *in vitro* studies
 27 typically are continuously bathed in high doses of the medication in question, while living
 28 creatures break down and excrete the medication. (Ahmed Tr., JX 65, at 125:10-23; REF. MAN. at

563-64.) *In vitro* studies also provide no information regarding a medication’s *net* effect on the human body – only the isolated, single effect being measured – and are categorically insufficient to establish that a substance can cause a particular disease in humans. “There are short-term *in vitro* tests for just about every physiological response and every organ system[.] . . . Relatively few of these tests have been validated by replication in many different laboratories or by comparison with outcomes in animal studies to determine if they are predictive of whole animal or human toxicity.” (REF. MAN. at 645; *see* Piazza Tr., JX 61, at 472:23-473:17 [“In addition to tissue culture studies, it is crucial to validate the *in vivo* roles of candidate targets . . . in animal studies for an accurate assessment of efficacy and toxicity.”].) As a result, “[c]aution always must be used in extrapolating results in tissue culture to effects in live humans.” *In re Rezulin*, 369 F. Supp. 2d at 428-29.

In light of the limitations of preclinical studies, the most reliable way to evaluate the effects of a medication is to observe directly clinically relevant endpoints in real patients. (*See* Singh Lipitor Tr., DX 56, at 127:9-23.) In discussing the Arozarena study, Dr. Marais explained, “you can create hypotheses using cell and animals which you can then test in humans. I think it would be dangerous to assume, which I think is that the word ‘extrapolate’ means, that what you see in a mouse is what – will be what you see in a human.” (Marais Tr., JX 71, at 98:14-99:11.) Plaintiffs’ experts do not dispute these limitations, and yet they offer opinions about humans based on the single, non-replicated *in vitro* result in the Arozarena study and the Dhayade study, without explaining reliably how and why they could have extrapolated their opinions from these “seemingly far-removed” preclinical studies. *Joiner*, 522 U.S. at 144.

C. Plaintiffs’ Experts Do Not Reliably Establish That The Dhayade Study Translates To Humans.

Plaintiffs’ experts do not reliably assess the undisputed limitations recognized by the authors of the Dhayade study. Their willingness to offer biological plausibility opinions in the face of those limitations warrants exclusion of their opinions.

1. The Dhayade Study Relied On Cell And Animal Models That Do Not Apply To Humans And Used Massive Doses Of PDE5 Inhibitors.

“In assessing the reliability of an extrapolation from *in vitro* results to effects in live humans, two crucial considerations are the type of cell on which the *in vitro* experiment was performed and the dose to which the cells were exposed.” *In re Rezulin*, 369 F. Supp. 2d at 429; *see Joiner*, 522 U.S. at 144-45 (affirming exclusion of experts who relied on animal studies involving exposure to “massive doses” of chemicals alleged to cause cancer in humans because the studies were “so dissimilar to the facts presented in this litigation”); *In re Bextra & Celebrex*, 524 F. Supp. 2d at 1174 (noting that the first central tenet of toxicology is the “dose makes the poison” and that “[e]ven water, if consumed in large quantities, can be toxic”). Plaintiffs’ experts’ methods fall short in both respects.

Plaintiffs’ experts rely on *in vitro* experiments in the Dhayade study that involved almost exclusively B16 mouse melanoma cells. (Piazza Rep., JX 5, at 19-23; Ganesan Rep., JX 17, at 14-16; Haq Rep., JX 9, at 17-18.) Plaintiffs’ experts agree, however, that B16 mouse melanoma cells do not have mutations of the BRAF or NRAS genes and therefore are not representative of the vast majority of human melanomas. (Piazza Tr., JX 60, at 57:3-18; Ganesan Tr., JX 56, at 151:16-20.) And the Dhayade study authors themselves recognize that the pathway they studied in B16 mice “is probably not universally conserved in all human melanomas.” (Dhayade, JX 87, at 2604; Feil, JX 104, at 1.)

Nor do Plaintiffs’ experts reliably explain how the extremely high doses of PDE5 inhibitors used in the Dhayade study apply to living humans. Plaintiffs’ experts concede that the *in vitro* experiments in the Dhayade study bathed the cells with doses of Viagra that were approximately 150 times the maximum daily dose in humans on a bodyweight basis, and 100 times greater than the Viagra dose used in the *in vitro* experiments in the Arozarena study. (*See* Piazza Tr., JX 60, at 168:5-171:25; *see also* Bastian Rep., JX 44, at 73.) Similarly, the only experiment in the Dhayade study involving the administration of Viagra in live mice gave mice a dose that was 180 times the maximum concentration in humans taking the maximum dose, and did so for nearly two weeks. (*See* Dhayade, JX 87, at 2605, Fig. 6F; Marais Rep., JX 27, at 43.) Dr.

1 Piazza claims the difference is not that great, but even he was forced to admit that the dose is at
 2 least 10 to 15 times the maximum human dose. (Piazza Tr., JX 60, at 209:17-210:7; Nair and
 3 Jacob, DX 40.) The Dhayade study authors acknowledged “it is not clear whether the sildenafil
 4 concentration used in our experiments is also reached in patients.” (Dhayade, JX 87, at 2607.)
 5 And despite using such high doses, the Dhayade study showed only a small increase in tumor
 6 volume in mice treated with Viagra compared to the control group. (*Id.* at 2605, Fig. 6F.)

7 Plaintiffs’ experts’ answer to this fundamental flaw in the Dhayade study is to claim that
 8 the dose was appropriate because it increased cGMP levels in the mice. (Ganesan Tr., JX 56, at
 9 139:2-19; Haq Tr., JX 58, at 199:25-200:14.) But as Dr. Haq admits, using a dose that is too high
 10 can result in off-target effects (*i.e.*, a medication can have other effects in animals that are not due
 11 to the primary action of the medication). (Haq Tr., JX 58, at 283:24-284:10.) As a result,
 12 Plaintiffs’ experts have not reliably ruled out the likelihood that such high levels of PDE5
 13 inhibitors had off-target effects, such as effects on other PDEs, which makes it impossible to
 14 interpret the Dhayade results reliably. (Marais Tr., JX 71, at 215:2-216:15.) In other words, the
 15 type of mice and doses of PDE5 inhibitors used in the Dhayade study are too “dissimilar to the
 16 facts as presented in this litigation.” *Joiner*, 522 U.S. at 144-45. Because Plaintiffs’ experts fail to
 17 justify their extrapolation from the Dhayade study to humans, their opinions about the study are
 18 unreliable.

19 **2. The *In Vitro* Experiments In The Dhayade Study Did Not Test Viagra**
 20 **Alone But Instead Combined It With A Chemical The Authors Only**
 21 **Speculate May Be Present in Human Melanomas.**

22 Another fundamental limitation of Plaintiffs’ experts’ opinions is that the Dhayade study’s
 23 *in vitro* experiments did not study Viagra alone. The Dhayade authors dosed the cells with a
 24 chemical called CNP to trigger precisely the effect they hypothesized PDE5 inhibitors would have
 25 (an increase in cGMP), and only then added Viagra. (Dhayade, JX 87, at 2605-06, Figs. 6C, 6D,
 26 7C, 7E.) As the authors themselves acknowledge, there is no known source of CNP in human
 27 melanomas; instead, the presence of CNP is speculative and the source of CNP in melanomas
 28 “needs to be established in future studies.” (*Id.* at Fig. S5.) None of Plaintiffs’ experts cite any
 study establishing a source of CNP in a human melanoma cells. As Dr. Ganesan explained, the

1 Dhayade study authors merely “speculat[ed] on what the source of CNP could be.” (Ganesan Tr.,
2 JX 56, at 37:14-22.) Plaintiffs’ experts admit that they do not know whether a PDE5 inhibitor
3 alone, without CNP, would have the same effect. (*Id.* at 37:3-38:5, 75:13-16, 161:1-9; Haq Tr.,
4 JX 58, at 189:10-190:16; 212:13-213:5.)

5 Expert testimony must be based on “more than subjective belief or unsupported
6 speculation.” *Daubert*, 509 U.S. at 590. An untested theory concerning a hypothesized biological
7 mechanism is not a reliable basis to establish general causation. *See In re Viagra Prods. Liab.*
8 *Litig.*, 572 F. Supp. 2d 1071, 1085-86 (D. Minn. 2008). Because Plaintiffs’ experts cannot
9 exclude the possibility that CNP explained the Dhayade study’s results, and instead must rely on
10 speculation to offer their biological plausibility opinions, their opinions are unreliable. *See*
11 *Carnegie Mellon*, 55 F. Supp. 2d at 1034 (finding the failure to exclude alternative explanations
12 for the data on which an expert bases his opinion departs from scientific standards and justifies
13 exclusion).

14 CONCLUSION

15 For the foregoing reasons, the Court should GRANT Defendants’ motion to exclude the
16 opinions offered by Plaintiffs’ experts.

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Respectfully submitted,

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APPENDIX

Table 3. Totality of Observational Studies – Melanoma Results

	<i>Li</i> (2014)	<i>Loeb</i> (2015)	<i>Lian</i> (2016)	<i>Matthews</i> (2016)	<i>Portegard (DNHR)</i> (2016)	<i>Portegard (KPNC)</i> (2016)	<i>Sokolov</i> (2016)
Ever used a PDES ¹	N/A	1.21 (1.08-1.36)	1.18 (0.95-1.47)	1.14 (1.01-1.29)	1.06 (0.96-1.18)	1.01 (0.91-1.12)	1.04 (0.98-1.12)
High PDES ¹ use (≥ 100 tablets)	N/A	N/A	N/A	N/A	1.22 (0.99-1.49)	0.95 (0.78-1.14)	N/A
Recent Viagra use	1.84 (1.04-3.22)	N/A	N/A	N/A	N/A	N/A	N/A
Ever used Viagra	1.92 (1.14-3.22)	1.14 (0.99-1.31)	N/A	N/A	N/A	N/A	N/A
Only ever used Viagra	N/A	1.26 (1.08-1.48)	1.22 (0.97-1.54)	N/A	1.08 (0.96-1.22)	1.00 (0.90-1.12)	1.02 (0.94-1.11)
High Viagra use (≥ 100 tablets)	N/A	N/A	N/A	N/A	1.15 (0.90-1.46)	0.86 (0.67-1.11)	N/A
Ever used Cialis	N/A	1.16 (0.99-1.37) Cialis or Levitra	N/A	N/A	N/A	N/A	N/A
Only ever used Cialis	N/A	1.30 (1.08-1.57) Cialis or Levitra	1.02 (0.72-1.45)	N/A	1.06 (0.88-1.28)	N/A	1.07 (0.98-1.16)
High Cialis use (≥ 100 tablets)	N/A	N/A	N/A	N/A	1.47 (0.99-2.18)	1.06 (0.79-1.41)	N/A
Viagra time- dependent use	N/A	N/A	N/A	N/A	N/A	N/A	0.98 (0.90-1.07)
Cialis time- dependent use	N/A	N/A	N/A	N/A	N/A	N/A	1.03 (0.94-1.14)
PDES ¹ time- dependent use	N/A	N/A	N/A	N/A	N/A	N/A	0.99 (0.92-1.06)
By number Viagra tablets	N/A	N/A	N/A	N/A	<20: 0.98 (0.80-1.19) 20-49: 1.08 (0.87-1.33) 50-99: 1.22 (0.92-1.62) 100-199: 0.98 (0.70-1.37) 200-499: 1.44 (0.99-2.11) 500+: 1.39 (0.58-3.32)	<20: 0.87 (0.73-1.04) 20-49: 1.13 (0.94-1.35) 50-99: 1.21 (0.96-1.52) 100-199: 0.80 (0.58-1.10) 200-499: 0.87 (0.56-1.37) 500+: 2.50 (0.91-6.88)	Each add'l 100 Viagra tablets: 1.02 (0.97-1.08)

PDES¹ = PDES Inhibitor Rx = Prescription

Table 3. Totality of Observational Studies – Melanoma Results

	<i>Li</i> (2014)	<i>Loeb</i> (2015)	<i>Lion</i> (2016)	<i>Mattheus</i> (2016)	<i>Portegard (DNHR)</i> (2016)	<i>Portegard (KPNQ)</i> (2016)	<i>Shkoljar</i> (2016)
By number Cialis tablets	N/A	N/A	N/A	N/A	<20: 1.10 (0.83-1.45) 20-49: 1.07 (0.75-1.53) 50-99: 0.64 (0.37-1.10) 100-199: 1.20 (0.71-2.05) 200-499: 2.05 (1.10-3.84) 500+: N/A	N/A	Each add'l 100 Cialis tablets: 1.06 (1.02-1.11)
By number PDE5I tablets	N/A	N/A	1-4: 1.17 (0.88-1.55) 5-24: 1.00 (0.75-1.32) ≥25: 1.34 (1.04-1.72)	N/A	<20: 1.06 (0.89-1.26) 20-49: 1.02 (0.84-1.24) 50-99: 0.95 (0.72-1.24) 100-199: 1.07 (0.81-1.42) 200-499: 1.44 (1.04-1.98) 500+: 1.47 (0.75-2.89)	<20 : 0.88 (0.73-1.07) 20-49: 1.13 (0.96-1.33) 50-99: 1.09 (0.89-1.33) 100-199: 0.80 (0.61-1.04) 200-499: 1.18 (0.90-1.56) 500+: 0.94 (0.45-1.97)	Each add'l 100 PDE5I tablets: 1.05 (1.01-1.09)
By number Viagra Rx's	N/A	1: 1.17 (0.96-1.44) 2-5: 1.16 (0.92-1.45) ≥6: 1.06 (0.79-1.42)	N/A	N/A	N/A	N/A	Each add'l 10 Viagra Rx's: 0.99 (0.94-1.05)
By number Cialis Rx's (Cialisor Levitra in Loeb study)	N/A	1: 1.12 (0.85-1.47) 2-5: 1.11 (0.86-1.44) ≥6: 1.29 (0.97-1.71)	N/A	N/A	N/A	N/A	Each add'l 10 Cialis Rx's: 1.02 (0.97-1.08)

PDE5I = PDE5 Inhibitor Rx = Prescription

Table 3. Totality of Observational Studies – Melanoma Results

	<i>Li</i> (2014)	<i>Loeb</i> (2015)	<i>Lion</i> (2016)	<i>Matheus</i> (2016)	<i>Portegard (DNHR)</i> (2016)	<i>Portegard (KPNC)</i> (2016)	<i>Shkoljar</i> (2016)
By number PDE5i Rx's for Mathews as listed in Loeb meta-analysis	N/A	1: 1.32 (1.10-1.59) 2-5: 1.14 (0.95-1.37) ≥6: 1.17 (0.95-1.44)	1: 1.15 (0.88-1.51) 2-6: 1.07 (0.82-1.41) ≥7: 1.30 (1.01-1.69)	low use (1 Rx): 1.15 (0.94-1.41) high use: 1.05 (0.78-1.41)	>500 doses: 1.85 (1.18-2.90)	>500 doses: 1.22 (0.89-1.67)	Each add'l 10 any PDE5i Rx's: 1.01 (0.96-1.05)
By Clinical Stage (PDE5i use; Portegard based on high use (≥100 tablets)	N/A	Stage 0: 1.49 (1.22-1.83) Stage I: 1.21 (1.02-1.43) Stages II-IV: 0.83 (0.63-1.09)	N/A	N/A	In Situ: N/A Localized: 1.21 (0.95-1.54) Non-localized: 0.75 (0.32-1.75) Unknown: 1.44 (0.92-2.24)	In Situ: 1.15 (0.95-1.41) Localized: 0.99 (0.81-1.21) Non-localized: 0.61 (0.30-1.23) Unknown: 0.98 (0.31-3.09)	Treatment for advanced disease: Lymph node dissection (p=.26), chemo (p=.66), radiotherapy (p=.38), metastasis (p=.39)
Pulmonary Hypertension: PDE5i use	N/A	N/A	N/A	N/A	N/A	N/A	Any PDE5i use: 0.74 (0.48-1.13) Time-dependent use: 0.65 (0.38-1.32) Each add'l 100 tablets: 0.64 (0.41-0.99) Each add'l 10 Rx's: 0.52 (0.26-1.04) Any PDE5i use: 1.03 (0.97-1.10) Time-dependent use: 0.98 (0.91-1.06) Each add'l 100 tablets: 0.99 (0.95-1.03) Each add'l 10 Rx's: 0.98 (0.93-1.03)
Lower Urinary Tract Symptoms: PDE5i use	N/A	N/A	N/A	N/A	N/A	N/A	

PDE5i = PDE5 Inhibitor Rx = Prescription

Table 4. Observational Studies and Meta-Analyses – Melanoma Primary Risk Estimates and BCC Risk Estimates

	Melanoma	Basal Cell Carcinoma
Observational Studies		
Li (2014)	1.84 (1.04-3.22)	1.08 (0.93-1.25)
Loeb (2015)	1.21 (1.08-1.36)	1.19 (1.14-1.25)
Lian (2016)	1.18 (0.95-1.47)	1.07 (0.99-1.16)
Matthews (2016)	1.14 (1.01-1.29)	1.15 (1.11-1.19)
Pottegard (DNHR) (2016)	1.06 (0.96-1.18)	N/A
Pottegard (KPNC) (2016)	1.01 (0.91-1.12)	N/A
Shkolyar (2018)	1.04 (0.98-1.12)	1.04 (1.00-1.08)
Meta-Analyses		
Loeb (2017)	1.12 (1.02-1.23)	1.16 (1.13-1.20)
Wang (2017)	1.12 (1.03-1.21)	1.14 (1.09-1.19)
Tang (2017)	1.12 (1.03-1.21)	1.14 (1.09-1.19)
Han (2018)	1.12 (1.03-1.33)	N/A
Feng (2018)	1.13 (1.04-1.23)	1.18 (1.11-1.27)
Deng (2018)	1.12 (1.03-1.21)	1.14 (1.09-1.19)

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing was electronically filed through the Court's CM/ECF system on January 11, 2019, which shall send notification of such filing to all CM/ECF participants.

/s/ Loren H. Brown
Loren H. Brown